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# ANNALS OF INTERNAL MEDICINE

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VOLUME VI

JUNE, 1933

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## President's Address\*

By F. M. POTTENGER, M.D., F.A.C.P., *Monrovia, California*

ONE of the greatest honors which can come to an internist in America is to have his colleagues entrust to his care and guidance the destinies of The American College of Physicians, for this organization stands for the highest ideals and the noblest sentiments which actuate medical men in the pursuit of knowledge and in the application of medical facts to the prevention and cure of disease, and to the alleviation of suffering. A year ago, on assuming the duties of President, I thanked you warmly for the confidence which you reposed in me, and tonight, I again wish to express my grateful appreciation for this high honor.

In accepting the honor, the President also assumes the responsibility of furthering the interests of the organization by keeping in touch with the members and studying their problems. In his Presidential Address he is expected to comment on the subjects which he considers of special importance to the College, either in conducting its inter-

nal affairs, or in advancing and upholding its standards in laboratory and clinical practice; or upon special problems which may confront the College at the time, or press for solution in the near future.

The internal affairs of the College seem to be in good order. Its position in American Medicine is unquestioned. It numbers among its members men who are representative of the best in research, teaching and practice. By the intimate association of its members medical knowledge is furthered, the enthusiasm of the members is increased, and friendships are cemented. While there are many fields in which our organization may direct its energies in the service of Medicine, it has seemed wise thus far to confine our efforts to strengthening our own organization. Heretofore our members have preferred to have the College stand for leadership in medical thought rather than in organization, yet questions of a vital economic nature are arising today both in Medicine and in the body politic which are forcing themselves upon us and calling for leadership in their solution. Would it

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\*Read at the Seventeenth Annual Clinical Session of the American College of Physicians, Montreal, Canada, February 6-10, 1933.

not be well for the members of the College to answer this call and give to the solution of these problems the aid of their well trained minds?

#### THE OPEN MIND

From the time of Hippocrates, interest in the study of Medicine has been stimulated by the fact that it has been a continuous excursion into the unknown. New fields to be investigated have required new methods of procedure and taxed the ingenuity of the curious. New facts obtained have called for imagination and patient observation to determine the manner in which they were to be utilized to improve conceptions already held.

One of the difficulties met in the development of Medicine is that which attends advancement in any unfolding science, that of putting a true value both on the ideas already held, and on the new ones which are advanced from time to time.

The medical mind can never become static. It is necessary only to look back a few decades, to see that ideas which were accepted as guiding principles, now, as a result of further investigation, are either greatly modified or wholly displaced. We have many facts which are safely grounded; and many more which, though accepted, are not fully proved.

The open mind in science is the only safe mind, the only mind that can be expected to progress and utilize knowledge as it is acquired. It is the mind which, knowing its limitations, receives new things sympathetically, critically, but with a readiness to displace prevailing belief, no matter how well it seems to be founded, by any new knowledge that may be definitely

proved. Thus, Medicine calls for an openness of mind and a criticalness of judgment such as it is almost impossible to attain. It demands a conservatism born of knowledge and experience, combined with the liberality of the adventurer who considers the known as never final, but always subject to change with increased experience.

Edison is credited with having approached new theories with a rare open-mindedness and to have classified them into two categories: one, that which agreed with what he believed to be true; the other, that which did not agree and so was to be investigated. It requires a well organized and controlled mind to classify data as agreeing or disagreeing with "*what one holds to be true or false*" rather than with "*what one knows to be true or false*." Such a man might never be able to speak with the dogmatism of authority, yet he would be a safe leader to follow, for knowledge to him would be an open book with every page unfinished.

Medical progress has come through continuous questioning. A leader who progresses along accepted lines and pushes the outposts of knowledge a little further than those previously established, but does not depart too much from the known, is readily followed by his confreres; but the leader who climbs over the sides of the groove which confines prevailing thought and constructs a bridge into the unknown, is followed by few. He at once meets opposition from those who are satisfied with their own beliefs and whose minds can not or will not follow.

There is a general belief that the human mind hungers for knowledge,

but it also must be apparent that it often shows a strong tendency to resist the knowledge which would satisfy the hunger; for, as has been so aptly said, "As a means of retarding the entry of unusual notions the human cranium is a well-nigh perfect mechanism." This was well illustrated in the slowness with which the works of Harvey, Jenner, Pasteur and Lister were accepted by the leaders of Medicine of their day, and in the hostility with which new ideas in the economic field have always been met by the followers of *laissez faire*. Original investigators who conquer the unknown generally receive their greatest recognition after they have passed on, but continue to receive it until the horizon becomes dimmed by time.

In this generation, progress has been made so rapidly in all fields of endeavor that even those who have added greatly to the sum total of our knowledge are apt to go unrecognized. We have many such who sit at the meetings of this Association. They walk among us so freely that we forget the contributions which they have made. We accept their gifts of knowledge with less ado than we accept gifts from friends; yet if a few score of these creative minds, with their contributions to science, were removed from the Medicine of the present generation, our profession would be comparatively barren of interest.

The members of the College have certain obligations to fulfill, not alone in Medicine but as leaders in this period of reconstruction which is upon us. A prime essential of leadership is an open mind, an ability to recognize the fact of an ever-changing present and envisage a future which will probably

be characterized by still greater change. One must be able to look forward for the solution to unsolved problems, not backward. The fundamentalist can not satisfy the inquiring mind of the present generation nor successfully solve the problems which confront it and future generations by looking back to the interpretation of moral and religious problems as given centuries ago.

#### TRENDS IN DEVELOPMENT OF PRESENT-DAY MEDICINE

The greatest advance which Medicine is making today is in the prevention of disease. The greatest advance in the domain of clinical practice is being brought about through a better understanding of its physiologic side. Until the immediate past, structural anatomy and structural pathology dominated the entire field. Symptoms which were unattended by recognized anatomical change were considered to be of no importance no matter how much they distressed the individual, and were ignored by able clinicians. Physicians regarded such symptoms with unconcern until sufferers began to seek aid from various irregular practitioners. This failure to grasp the importance of disturbed function is almost incomprehensible today, because the practice of Medicine is centered about a desire to understand the cause of symptoms, and to apply remedies which will relieve them.

Just when Medicine appeared to be definitely established on a structural basis, and organic lesions seemed to be secure in their occupancy of the entire stage of interest, a disturbing element entered in the form of new developments in the field of physiology. Advances in biophysics, biochemistry,

neural physiology and endocrinology came swiftly to the fore, and the importance of psychic reactions became appreciated as never before. We then learned that many of the symptoms which physicians are called upon to treat are changes in function without structural change in the organ showing the physiologic disturbance. We were then able to appreciate the ridiculousness of such statements as were current but a short time before to the effect that 90 per cent of the patients who visit doctors' offices have nothing the matter with them.

Physiologic studies emphasize the fact that the human organism is a united whole, in which the action of any one part may be influenced by every other part; and physiologic balance and imbalance now begin to assume great importance in the definition of conditions of health and disease. The cause, whether constitutional, environmental, structural, physiologic or psychologic, matters less than the fact that the patient is ill.

Approached from this angle, Medicine becomes a more rational study. It becomes both a physiologic and anatomic study. The fact that constitutional factors determine to a large degree the manner in which a given individual will react to environmental stimulus now becomes evident.

The nervous system, both somatic and vegetative components, each in its integrative action in its own separate field and in the interplay between skeletal and visceral structures now assumes an unexpected importance, not only because of its central reactivity to chemical and physical stimuli, but also because of its function in producing physiologic and pathologic reflexes.

Only by developing a more accurate knowledge of the vegetative nervous system can we understand the efficient correlating mechanism by means of which unity of action is brought about and maintained in distantly separated organs through centers in the brain and cord both during conditions of health and in states of disease.

Hormones, vitamins and salts, in normal proportions, as circulating regulators of cellular activity during health, and, in abnormal proportions, as disturbers of cellular activity during illness, become important determining factors in many aspects of physiologic and pathologic function. The electrical reactivity of cells seems to hold much in store for explaining body reactions, although as yet it is vague in the minds of most investigators. The pH of the tissues also bulks large in importance.

In physiologic Medicine, psychic reactions assume a prominence in the health of individuals which approaches in importance that of structural change, and which often proves to be of greater importance to their happiness. No matter what the disease, it has its psychic component which will either help or hinder recovery.

Physiologic Medicine is more difficult to comprehend and develop than anatomic Medicine, but medical science and practice can not be rounded out until this subject has been thoroughly investigated. It is more elusive and more erratic than anatomical studies. There are more variables in each problem. The field of study can not be embedded in a fixing solution and prepared for microscopic investigation. Physiologic reactions are subject to all changes which depend on inherited and acquired constitution, and on the adap-

tation of the living processes to environment in its broadest sense—both internal and external, both physical and psychical.

The rapid decrease in mortality in early life has permitted many with weak constitutions, who formerly would have succumbed to disease in infancy and childhood, to live and attain the age in which the human machine shows more plainly the effects of wear and tear, the age in which the degenerative diseases hold sway. This has forced Medicine to become increasingly interested in the patient as well as in the cause of the disease and the cellular changes produced by it.

Inherited qualities; physical and chemical constitution, as determined at birth and modified by environment; correlation and integration of activity through the hormones and nervous systems; and lastly the psychical structure of the patient now call for as full consideration as cellular pathology and the cause of infectious disease did but a short while ago. This shift adds a new, and in the minds of many men a greater, interest to Medicine.

Heredity, although its meaning was poorly defined, had been considered to play an important part in certain diseases prior to the time that their etiology was discovered; but, as specific causes, one by one, were discovered, heredity was forced for the time being to occupy an insecure position. With greater fundamental knowledge, however, we are learning that heredity plays some part in all diseases, and a very important one in many.

We assume that to attain old age one must be endowed with an anatomic and physiologic mechanism which adapts itself well to the work that it must do,

and meets the changing requirements of environment in a satisfactory manner; and further, that it does not become incapacitated by misuse, abuse or illness.

If the individual passes through early childhood, the chances are greatly in favor of his reaching adult life. Among those who attain adult life are many who are fit to live only because conditions have been made especially favorable for them. On the other hand, we must look upon the attainment of advanced age by most people as being due to a better, more virile stock. Captain MacMillan, the arctic explorer, once told the writer that the survivors of lost expeditions in the arctic were not saved by accident, as is commonly believed, but that their survival was evidence of a better heredity, a more rugged stock. He further said that nearly all such survivors, instead of having their bodies weakened by the exposures and hardships, endured them without apparent injury and lived to a "ripe old age".

#### SPECIALIZATION

One of the very interesting and important phases in present-day Medicine is the development of the specialist. While specialization is not new it has become a dominating characteristic of the Medicine of the last quarter of a century. It is the natural sequence of fruitful, systematic investigation.

With the rapid advance in knowledge at the turn of the century so many new facts were being brought forth that specialists became necessary in order properly to apply them to research and practice. When we behold the present highly specialized status of Medicine it is difficult to realize that

we are only one generation away from the general practitioner who applied, in treating the patient, all of the facts that were then known to all of the diseases that were recognized.

During the past quarter of a century keen observers have interested themselves in nearly every individual phase of Medicine; individual diseases, diseases of individual organs and systems, even symptoms caused by certain body reactions. They have set these subjects apart for special study, picking out the data which bear particularly upon the subject under investigation.

Individual men have chosen for special study those phases of Medicine which have appealed to them most, and so have added a sympathetic interest, which accounts for much of the rapid progress. Once started, the idea of specialization grew rapidly. It seemed impossible for single minds to comprehend and accurately weigh the new facts which were being added to the sum of medical knowledge and to apply them to medical subjects as a whole. Only through the study of limited fields was great success possible. By intensive specialization, in the short space of two or three decades, our knowledge of many subjects has been well systematized and our opinions and impressions have been replaced by facts.

We are today so accustomed to being directed and protected by the laws of public health, for example, that it seems as though this important phase of Medicine, calling as it does for highly trained specialists, must always have existed; yet the public health official had little scientific background and small reason for existence until the latter part of the nineteenth century,

when bacteriology developed and the theories that disease was due to supernatural powers and miasmas were displaced by actual proof of the cause of contagion.

Specialization during this developmental period threatened General Medicine with disaster. Its influence was largely disintegrative. It tore Medicine asunder, divided it up into many parts and attempted to create many separate entities. But strange to say this disintegration finally checked itself and resulted in a demand for a new assessment of values; for, as each specialty developed further it became more and more apparent that it was not a separate medical entity but only a part of Medicine as a whole, and a much more intimate part than some of the earlier specialists realized.

We now find that each specialty has resulted in enriching Medicine as a whole to the extent of its individual development; and Medicine, divided by the multitude of specialties during the period of their development, is now being reunited into a completed whole in which the internist is able to render a greater service than the specialist could give but a few years ago. That this process of unification and coördination is well under way is evidenced by the high character of service which is now being rendered by internists in fields which were limited to specialists but a short time ago.

Specialists will probably always be necessary, but their position will doubtless change. In the future the specialist, in the more restricted sense of the term, will probably assume the rôle of consultant in his particular line, and internists will specialize in those subjects which interest them predominant-

ly, but not to the exclusion of other phases of Medicine. In this way the narrowing tendency of specialization will be checked.

#### THE INTERRELATION BETWEEN MEDICINE AND GENERAL ECONOMICS

Much of the recent discussion of medical economics has not taken sufficiently into account the relationship of medical problems to the general economic condition.

The relationship which Medicine bears to the public was established before the birth of public health with its life-saving campaign and before the advances in science and technology were allowed to destroy the stability of industry. The logical solution of the problems of medical economics depends on the solution of the problems of general economics. If the state is to control industry, it will and probably should control Medicine. If, on the other hand, we are able to maintain the principle of individual effort in industry, it is but justice that the same principle should be applied to Medicine. Just at present, however, it appears as though Medicine were being forced to make an adjustment to an unadjusted and an admittedly unsatisfactory general economic system. If an open mind were ever needed in the solution of problems in Medicine, it is today.

The rapid development of modern Medicine has been made possible through advances in the cognate sciences. This in turn has called upon those desiring to practice Medicine or to engage in research to spend much time and money in preparation. It requires of the student who would fit

himself for the practice of Medicine an expenditure of from ten to fifteen thousand dollars, and the loss of earning power for the seven to ten years spent in study, a total of some \$15,000 to \$25,000.

While the cost of medical education has been increasing in recent years, changes have been going on within Medicine itself, as well as in our economic system, which tend greatly to alter the status of the profession; and, with present trends, to make its position in the body politic insecure. This situation is growing more and more serious, and must be carefully considered by present practitioners and prospective students.

Physicians are attempting to carry out principles of altruism, living ethical lives and following high traditions, in a competitive age which is characterized by uncontrolled ambition for profits. Laymen do not understand the motives which underlie the ethical acts of medical men. The aims and methods in Medicine are so foreign to those prevailing in business that it is impossible to furnish the laity with an intelligible explanation of our course of action. Were a business concern to foster methods which would limit its chances of economic success, the act would be looked upon as being not only foolish but one of insanity; were a business firm to refuse to take on a new purchaser because he was a regular customer of another firm, the act would be considered as contravening all business principles. On the other hand, were business concerns to adopt the altruistic spirit of physicians and take less profits, or no profits at all, from those who are unable to pay for their goods, it would soon change the

ruthless psychology which dominates modern economic life. Medical men do all of these things regularly as a part of their ethical standards.

Sentiment causes physicians to give their services to the sick poor without compensation. This they do gladly because they realize that they are not dealing with inanimate substances such as merchandise, but with human beings. Unfortunately, however, this very altruism exaggerates an already firmly established belief in the minds of laymen to the effect that medical service costs the doctor nothing, and that it is the province of Medicine to care for those for whom our present economic system fails to provide. Those ideas should be corrected, for they prevent the physician from being adequately compensated. Laymen should be made to appreciate that lengthened life, decreased morbidity and increased efficiency through relief from illness have a monetary value.

We shudder at the idea of State Medicine, yet under recent economic conditions during normal times the state furnishes medical care for a large percentage of the population, **some** justly, some unjustly, or at least questionably; as for example, veterans of the World War whose illness has no connection with service. Medical men vie with each other for positions on the staffs of charity hospitals where they give their services without remuneration. Many students of the subject put forth the argument that it is not fair that, of all services to the

poor, medical care alone should be furnished without cost. State Medicine, sick and accident insurance, unemployment insurance, old age pensions and group care are some of the many plans that have been suggested to insure adequate medical care to those who can not readily pay for it out of their earnings. Whether medical men are favorable to the idea or not, unless adequate changes are quickly made in general economics, some of these plans will be adopted. To the extent that they contravene the individual relationship between physician and patient they will be unsatisfactory; to the extent that they guarantee a better medical service to the people and give more adequate remuneration to the physician for services rendered they will be acceptable.

Perhaps there is no better way to obtain an idea of the problem of medical economics and no way better to judge the ability of people to pay for medical services than to study the incomes of groups of the population. Numerous surveys have been made, but I shall use the data obtained by the Commonwealth Club of San Francisco in 1931, and that acquired by the Committee on the Cost of Medical Care. Let me say, in passing, that conditions in San Francisco are much more favorable to the working classes than in many other cities of the country, for labor has had a large share in the government of this city.

The following is the grouping of incomes as brought out as a result of the San Francisco survey:

14 per cent of incomes were less than	\$1,000
30 per cent of incomes were from	\$1,000 to 1,500
35 per cent of incomes were from	1,500 to 2,000
14 per cent of incomes were from	2,000 to 3,000
5 per cent of incomes were from	3,000 to 5,000
2 per cent of incomes were over	5,000

If these statistics are analyzed from the standpoint of the population's ability to pay for medical care, it gives little comfort to physicians.

There is no fixed standard by which we may determine who can pay for medical services, and what the fee should be. It is supposed to be based upon the financial status of the patient, but this is determined not alone by the amount of a given income but by the demands made upon it. An unmarried individual without dependents naturally can pay a much larger fee than the head of a family with the same salary.

That portion of the population with dependents to care for, who receive salaries below \$1,500 a year, are not in a position to pay very much for medical care, for it is estimated that bare necessities cost about \$1,500 per year for a family of four persons in the larger coast cities. Unless more than one member of the family is working, those belonging to this group are forced to obtain most of their treatment in free clinics and public hospitals.

The 35 per cent of people with incomes from \$1,500 to \$2,000 with dependents to care for, should be able to finance ordinary illness requiring only a few visits of the physician, but long illness, or illness requiring the services of medical or surgical specialists, could not be financed except by markedly reducing the family's living standard.

Thus we have 79 per cent of the population of San Francisco, according to these statistics, who are unable when ill freely to consult physicians. This leaves 21 per cent of the people who might be considered as able to pay for medical care.

Now, turning to the findings of the

Committee on the Cost of Medical Care, we find that, based on a twelve months' survey made during 1928-1931, the combined earnings of the members of 50 per cent of the families in the United States amounted to less than \$2,000 a year, and of 40 per cent, amounted to from \$2,000 to \$5,000. Their report also shows that 80 per cent of individuals had incomes less than \$2,000; and 95 per cent, less than \$3,000. One fact which was brought out by the report is that 4 per cent of the families with incomes under \$1,200 per year, collectively, spent as much money for medical care as 80 per cent of the same families, collectively. This is discussed along with other findings and interpreted as showing that the uncertain cost of medical care and the inability of the people to meet such cost readily is deterring people with small incomes from freely consulting physicians. If medical care is a necessity, however, as we certainly believe it to be, this should be interpreted as showing that people do not have sufficient income to pay for the necessities of life, and should call for adjustments in general economics rather than sacrifice on the part of physicians, for the same people are unable to supply themselves adequately with other necessities such as food, clothing and shelter.

Public health and sanitary science, by creating a better environment to live in, have protected and strengthened the race, lowered the incidence of disease, and markedly reduced mortality. Based on these facts optimists have dared to express the hope that infectious disease may be eliminated from the face of the earth. Whether such a desideratum may or may not be accomplished, at least every increase in bac-

teriology and epidemiologic knowledge, and every advance in sanitary practice brings such an accomplishment nearer of attainment; and, simultaneously, restricts further the field of medical practice.

General mortality has been reduced 50 per cent during the past 50 years, infant mortality 60 per cent in 20 years, and life expectancy has been increased from 40 to nearly 58 years in the past 40 years. Where only one-half of the population could expect to survive the eighteenth year one hundred years ago, one-half of those born today may expect to live to be 66 years of age; and one-fourth, 76.

While the population, as a whole, has greatly profited by these accomplishments, medical practice and economics have undergone changes which demand readjustment. Physicians have been deprived of a large source of practice among children whose medical care is paid for by parents during the most prosperous period of their lives. They find themselves instead treating an ever-increasing number of older people during the period of declining efficiency, when their earning power is decreasing and when, too often, they have already reached a state of dependency. Also they find themselves treating an increasing number of people with small incomes and an increasing number of the unemployed.

The reduction in illness and mortality in early years, and the rapid increase in life expectancy, have not only brought about important changes in the trends of study, practice and economics of Medicine, but at the same time have exerted a definitely disquieting influence upon the general economic

condition of the country. These influences are so subtle that they have scarcely been appreciated, and therefore have not received the attention which their importance demands.

At first glance it would seem that the effect of an increasing number of people reaching adult life should be favorable to medical practice, and this would be the case if continuous employment at adequate wages were obtainable for all, so that physicians might be freely consulted when sickness arises; but, unfortunately, the number of people who are competing for employment is increasing at a time when, on account of the changes in our industrial system, fewer workers are required. Chase says that every census for an hundred years showed an increased number of men in the factories until the late war, after which production has gone steadily up, increasing 70 per cent between 1914 and 1927 with the number of employees as steadily decreasing. While 1929 was the peak year of production in industry in the United States for all time, yet there were one million and a quarter more workers idle than in 1923. We are saving lives and enabling men to live to old age, but are not making provision for them in our economic system. Therefore, increased longevity may prove to be a curse to those who attain old age, and it may throw an added burden on the physician in the way of more illness to care for without increase of his compensation.

As has been seen, workers who receive \$1,500 and less per year represent a very large proportion of our population. As an example we cite the shoe industry, which in 1925 paid an

average annual wage of \$1,090 per worker. Workers reach their highest earning capacity at the age period of 43 to 55, after which their earnings decrease; and since the earnings for most of this class have been barely sufficient for necessities during their most productive period, savings for sickness and old age have been scant or have amounted to nothing at all.

We may appreciate the effect which a shift of a large portion of the population to the higher age periods may have upon the medical profession, and also on the general economic condition of the country by determining the proportionate changes which the percentage of the people in the various age brackets has undergone in recent years. Fortunately we have for comparison the statistics of 1870 and 1920.

In 1870, when mortality in childhood and adolescence was high, the death rate was so great that 49.5 per cent of the population was in the age period from birth to 19 years. By 1920, largely through the application of preventive health measures, so many more people had already lived through childhood and adolescence and passed on to adult life that only 40.3 per cent of the total population were found between the ages of birth and 19 years. In the same 50 years the percentage of those between 20 and 44 years had increased from 12.6 to 16.9 per cent, and those above 65 from 2.9 to 4.5 per cent of the population.

The significance of this shift may be clearly seen by reducing the changes to percentages of the 1870 population.

During the 50 year term, the percentage of the total population included in the age-group from birth to 19

years decreased 19 per cent. The percentage of the population from 20 to 44 years, during these same 50 years, increased 9.4 per cent; giving 9.4 per cent more workers for whom employment must be provided during this most productive period of life. Those from 45 to 64 years increased 34 per cent, furnishing another very large group for whom work must be found; and those above 65 years increased 55 per cent, more than doubling the number of people in this period in which dependency and illness are most frequent. During this same period immigration also brought many workers into the country to compete for employment.

The shifting in age groups will become still more serious when, as we are told by statisticians, in a few more years our population becomes stationary and the younger group will constitute only about 30 per cent of the population, while 10.7 per cent, an increase of 138 per cent over the figures for 1929, will be over 65. The stationary period in the growth of our population will be hastened by the stop which has recently been put to immigration. Industry must take this reduction in purchasing power of future domestic consumers into consideration.

In order more fully to appreciate the interrelation between medical and general economics, we must examine the changes which have been wrought in our general economic system and the factors which have been responsible for them.

For four thousand years prior to the discovery of steam power there had been practically no change in man's productivity. Handicraft ruled the

world. There was no machine problem. There were no labor crises. There was no game of industrial warfare.

Steam ushered in a new era, and caused machines driven by the new power to compete with handicraft. In these early years the machines were thought to be inventions of the devil and were feared by the workers; but none realized the extent of the economic changes which were to be brought about by them in a fully mechanized age.

In the middle of the nineteenth century the effect of steam on industry was well established. At first machines were confined to a few industries and to industrial centers, and invention was directed toward increasing the production of those things which were necessary for man's welfare. The result was a ready consumption at home and available markets nearby for the surplus. This was the dawning of a new era in which human comforts were increased, and a new plane of living was ushered in.

Modern science, however, has made invention a plaything, and the world the market for its produce. Machine after machine has been invented, the sole aim of which has been to make more goods, not necessarily because they were needed, but because they offered profit to the inventor and those who were associated with him in their manufacture. Production is no longer wholly directed toward supplying man's needs, but toward supplying luxuries and satisfying man's whims. With special high-pressure salesmanship adapted to each article, accompanied by installment buying, almost anything has become salable, and people of mod-

est incomes have enjoyed comforts and luxuries as well as necessities.

Man power up to the time of the introduction of steam was considered to be equal to one-tenth horse power. On that basis the energy value of the adult male population of the United States today would be 3,600,000 horse power, but it actually is 1,000,000,000 horse power.

Many statistics of machine efficiency have been cited in current literature to show the extreme to which man power displacement has gone. These are passed over as fantastic by the more conservative; they are accepted at face value by the radicals; and are being considered as worthy of impartial investigation by a large mass of our people. While these statistics have been criticized by some investigators as being incorrect in certain details, that they are correct in principle is not questioned, and that our social and economic systems have not taken sufficiently into account the unemployment caused by the machine, nor made adequate adjustment to the various changes which the revolution in industry has brought about, is also unchallenged.

The following examples will illustrate the point:

For centuries one man could make about 450 bricks in a day; today a modern brick plant will make 400,000 bricks per man per day. For centuries a man could make one and a half barrels of flour per day; a modern flour mill will make 30,000 barrels of flour per man per day. The flour industry in 1899 was represented by 9,000 plants, employing 32,000 workers and utilizing 471,000,000 bushels of wheat. The number of plants increased to

11,700 in 1909; but in 1929, the number had been reduced to 2,900, employing only 26,400 men but utilizing 546,000,000 bushels of wheat. In 1900 the steel industry in the United States produced 11,000,000 metric tons of steel, requiring an energy of 600,000,000 man hours, which was equal to 70 man hours per ton, in 1929 the industry produced 58,000,000 tons, using 770,000,000 man hours, or at the rate of 13 man hours per ton.

So it goes on down through the whole field of industry; one man and a machine doing the work of many, and casting off those who are displaced to find new jobs or to join the unemployed. Each advance in science, and each new invention, makes adjustment in the established order necessary and opens up new possibilities for further scientific advance and invention. This calls not only for readjustment in industry, but in the social and economic spheres as well. It is not rational that science and invention should work harm to civilization, but by the failure to make proper adjustments the very foundations of our social and economic systems are being threatened. Did the late President Roosevelt have an inkling of what was going on when in 1918, to the query as to how long the present government of the United States would last, he replied: "Not to exceed fifty years".

The above striking illustrations of modern mechanization by no means reveal the end of technical possibilities. They show the inevitable trend of invention and mass production toward the displacement of men, but so long as existent industries, or industries newly established, were able to absorb

the displaced workers readjustments were effected. During the past decade, however, regardless of the establishment of new industries, unemployment has increased. Unfortunately, invention is displacing the skilled artisans and putting industry in the hands of machines and unskilled workers. While the products may be better, the machine has become the producer and the skilled worker has been degraded.

The present-day program of industry aiming at mass production also calls for large combinations of capital to insure distribution. It drives owners of smaller, independent businesses to the wall because of their inability to compete with larger companies, a policy which is rapidly eliminating the great middle class, the class which has shown the greatest appreciation of medical service and has given physicians their surest and most satisfactory return, the class which has always been recognized as the backbone of democratic nations. The independent merchant, the small manufacturer, and the farmer who owns his farm are being displaced one by one, for they have no place in the new order. They have been ruthlessly crowded out of the picture with nothing to compensate them or the nation for their loss. If the middle class is to have no place in a thoroughly mechanized society, then something must be devised to take its place. No people can be happy, nor can a nation long endure, if only a small percentage of the population who control industry are independent, while the rest are dependent upon them.

The rapidity with which production is shifting to large corporations is amazing. The small unincorporated

manufacturer does only 5 per cent of the manufacturing of the country today. In Illinois, in 1909, the individual owner employed 10 per cent of wage workers; and in 1919, 5.5 per cent, a decrease of nearly 50 per cent in 10 years. In the same state, in 1928, the net profits of all incorporated manufacturers was \$5,280,000,000; that of individual manufacturers was \$210,567,000, only 4 per cent of the total. This tells the story of the small independent manufacturer. Add to this the story of the independent farmer. We have boasted that American farmers alone in all the world have never been of the peasant class; but during the twenties, when all industries exclusive of agriculture were having the most prosperous years ever known, the farmers were in dire distress, were rapidly losing their farms and independence, and were sinking into a state of despair. The average net income of the 6,668,681 farms in 1929, for use in meeting the expenses of "capital, management and family living," was only \$847 per farm; and this had dwindled to \$342 per farm in 1931, and was probably about 25 per cent less in 1932.

Mass production, governed by competitive regulation, affects the employer as well as the worker, the difference being one of degree. It forces costly changes in productive plants, that each may be kept at the highest production efficiency, and is responsible for recurrent periods of saturated markets followed by inevitable unemployment, and shrinking in capital values. In 1929 there were 2,250,000 workers idle and 513 persons with incomes of over \$1,000,000 reported in the United

States; in 1931 there were 11,000,000 workers idle and 75 persons with incomes over \$1,000,000; while at the present time it is estimated that there are 14,000,000 workers idle and an equal number working only one-half time, with only a few individuals having incomes of \$1,000,000 a year.

Inventive genius and the genius to establish large combinations of capital in production and distribution, if uncontrolled, can produce only industrial instability and social unrest; if properly guided, on the other hand, they could be made into forces for a greater civilization.

The fact that the number of people above 65 years of age has increased so markedly in recent years requires that our economic system make adequate provision for workers both during their productive period and in their declining years; otherwise, public health measures become a mockery, and work an injury rather than a blessing.

The following statistics show with what rapidity unemployment is increasing in workers beyond 65 years of age. In 1890, 26.2 per cent of the male population over 65 years of age was idle; in 1920 the percentage was 39.9 per cent, an increase of 52.23 per cent in 30 years. We have no statistics at hand which give the amount of forced unemployment among the older workers which took place preceding 1929. We do know, however, that in 1929 there were 2,250,000 wage earners idle in the United States, an increase of more than 1,000,000 over the number idle in 1919; and we further know that the age group above 40 contributed more than its natural proportion to this

number, and that the proportion of those above 65 was likewise very exaggerated.

The increased amount of illness which affects those of the higher age groups makes it much more difficult for them, when once they lose their positions, to secure employment again. For those beyond 65 it becomes almost impossible. Even the insurance against illness which is supposed to work in favor of the employee works against the older man, for he is too apt to become a beneficiary to make him profitable to the employer, or to the insurance company.

Businesses of all kinds recognize that young, alert workers are able to accomplish more than those in declining years. While age may bring with it an improved judgment, modern technology leaves little place for judgment on the part of the worker. In vast commercial combinations judgment is furnished by overseers with exceptional technical training; very often by men who have no interest in the organization for which they work, except that of salary. The particular ability which calls for special monetary reward in the present economic system is that of supplying capital, organizing the business and choosing trained experts to do the technical work.

Since the economic prosperity of the nation depends upon maintaining the proper balance between production and consumption, we can turn back and hear the death knell of prosperity sounding a decade before the crash of 1929 came; but it fell on deaf ears. Productivity was fast outstripping wages. It had increased 54 per cent but wages only 30 per cent between

1900 and 1925, and by 1929 productivity in manufacturing had increased 90 per cent and wages only 40 per cent. Even with this enormous productivity manufacturing plants were running at only 60 per cent of their capacity. Such a divergence between productivity and wages caused a corresponding lag in consumption of goods which could only be remedied if those who received the difference in remuneration should consume the excess in goods, or failing this, if the commodities should be absorbed in foreign markets; neither of which was possible.

Since mass production calls for mass consumption, every idle man causes the loss of the consuming power of himself and those dependent upon him. If the 40,000,000 or more idle men in Europe and America, of whom at least 14,000,000 are in the United States, could be put to work at reasonable wages today, their consuming power would start all essential industries going. Indeed, what can start industry going other than an increased demand for goods? A prominent industrialist, keenly interested in the unemployment situation, recently stated that on account of the increased productivity which has been brought on by our modern industrial methods, we shall not have full time employment for our 48,000,000 workers in the United States for some years to come, probably never. Such a statement, if true, calls for complete industrial readjustment.

A machine driven by one man may do the work of ten or twenty men, and many will do that of a hundred; yet even so, there may be an enormous loss to the employer as well as to the workers who are thrown into the un-

employed ranks, unless, at the same time, provision is made for the consumption of the goods which the displaced 9, 19, or 99 men, with their families, would have consumed.

The most dependable market is made by employed workmen. They are far more important as consumers than the 2,000 directors of the 200 corporations in the United States which are said to control from 35 to 45 per cent of the business wealth, for the latter can not consume from 35 to 45 per cent of the goods produced.

Crises have recurred periodically since machine power became prominent in industry, but have become more frequent and more severe as efficiency in production has increased, and as world problems have become more complex. The aftermath of the World War has been partially responsible for the severity of our present economic crisis, but not the cause of it. Nevertheless international adjustments would greatly facilitate economic recovery. Many believe, with Lloyd George, that the present is not just one more recurrent depression but an indication of the total breakdown of our social and economic systems.

The United States has about 6.2 per cent of the population of the world, but it has 50 per cent of the world's energy. It has been calling upon its natural resources; its forests, coal, oil, natural gas and iron with unpardonable prodigality. It has ignored its agricultural class until it has driven the farmers to ruin. It has been the most active nation in applying science and invention to industry, hence has shifted the major portion of its population from the country to the city. It has

equipped its manufacturing industries so as to be able to produce enough goods for a great proportion of the world's population. In its mad onward rush it has neglected to make necessary adjustments in the social and economic life at home, and has also failed to take sufficiently into account the fact that other nations were also taking advantage of science and invention and equipping their industries for satisfying most of their own wants, and were also bidding more and more for foreign markets. So, just when equipped for an unwarranted production of goods, markets were found wanting, and industrial stagnation supervened.

During crises workers suffer a reduction in wages and lose their positions, capital becomes unremunerative, industrial plants remain idle and deteriorate, and distributing systems cease to function. Depressions are spoken of as inevitable. They are no more inevitable than the plagues of old. They call for scientific investigation and purposeful action; not mute acquiescence. They may be prevented if an altruism which recognizes human rights as being supreme, and the opportunity to supply the necessities of life by work as being an inalienable God-given right is made to pervade the industrial and economic world. Every man who wants to work should have employment. We must get away from the idea that every man in industry who can not do the maximum amount of work is waste. Every man is a potential consumer of goods, and all else being equal the larger the salary of the working man, and the more workers employed, the greater the consumption of goods, for their weekly incomes

represent their weekly expenditures. Every idle man, on the other hand, is a burden on some one, either temporarily or permanently.

The requirements of greater combinations of capital which characterize the "machine age" have put into the hands of the bolder and keener business men an undreamed of opportunity for the accumulation of profits and hoarding of wealth. These men by nature are neither worse nor better than the small manufacturers, merchants, and workers whom they have displaced. It is not against men that remedial measures are to be directed, but against the system which fails to recognize the rights of all men. Stripped of its glamour, the accumulation of great wealth is neither necessary nor desirable. It gives an unnecessary advantage to its possessor which few, if any, are able to use wisely, and worst of all creates an aristocracy based on power to command rather than on ability to do.

Many remedies for our present economic maladjustment have been proposed, each attempting to satisfy certain principles held most important by the one who makes the suggestion. Is it to a new order that we must look, such as socialism, communism, or fascism; or may a satisfactory solution be brought about, as many of us hope, through a modification of our present capitalistic system which will make it meet the requirements of the population as a whole, giving collective protection while preserving individual effort?

It is evidently impossible to make the same economic ideas that we held a century ago fit into the new order which has been ushered in by modern

science and invention. We must not try to cure a body politic suffering from systemic infection by directing our attention to a single organ. We must have the body economic examined by the most competent specialists to be found, and when they have catalogued and analyzed the symptoms and arrived at a comprehensive diagnosis, have our statesmen devise effective remedies, which will permit each social and economic group to develop to a maximum degree and render the best possible service to the people. It is useless for Medicine or any other single group to attempt to adjust its affairs to the present unsatisfactory general economic state; on the other hand, it is the duty of Medicine to join with other social and economic groups in bringing about a complete reappraisal of our entire social and economic system.

The experience of Medicine by which it was removed from the chaos caused by belief in spontaneous generation and miasmas, and in a brief space of time put upon a scientific basis by a few great leaders, such as Virchow, Villeman, Pasteur, and Koch, should suggest the way out of our economic distress. Leaders alone, however, can not produce the results. It requires followers possessed of open minds in whom the spirit of progress is held in greater esteem than are established opinions. General economics is still in the age of plagues and miasmas. It is waiting for a scientific awakening. It is calling for statesmen with the same originality as that shown by our great leaders in Medicine. Such leaders must be imbued with the same belief in human rights which has actuated those who

have met other great crises in history. The rights of all people must be paramount, and more "golden rule" and less "gold rule" must enter into the solution.

The scientific methods which have been applied to modern industry should guarantee to all of the people of the world a greater degree of economic security and the continuous enjoyment of a better health, a greater happiness, and a higher type of physical and cultural attainment than has ever before been possible. Unfortunately, however, we have been rushed from one

achievement to another with such precipitous haste that we have failed to adjust our progress to man's requirements. We are idle in the midst of the greatest producing devices in the history of the world; we are hungry and cold in the midst of abundance of food and clothing; and the wheels of industry are blocked although backed by the greatest concentration of wealth known to man. How to harness science for the good of mankind and not allow it to run on to his debasement and destruction is the burning question which this generation must settle.

## Observations on Addisin in Diseases of the Blood\*†

By ROGER S. MORRIS, F.A.C.P., MURRAY L. RICH, LEON SCHIFF,  
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IT has been demonstrated<sup>1,2</sup> that the normal stomach in man, swine, dogs and cattle secretes an hemopoietic substance which, when properly concentrated and purified, may be injected intramuscularly into man. This substance is thermolabile, dialyzable through colloidion, and exhaustible, and may be converted to an ethyl ester and extracted with non-aqueous solvents (ether, acetone, chloroform) without impairing its hemopoietic activity. These properties, which characterize both the material obtained from human gastric juice and that from the gastric contents of swine, practically exclude the possibility of its being an enzyme. It is probable that it is a physiological hemopoietic hormone, for which we have proposed the name *addisin*. Without sufficient evidence to enable one to arrive at definite conclusions, it seems likely that *addisin* is identical with the "intrinsic factor" of Castle<sup>3</sup> and with "hemopoietin" of Wilkinson,<sup>4</sup> a substance expressed under high pressure from the stomachs of swine.

Practically pure gastric juice has

been obtained from man through a stomach tube and from dogs through a gastric fistula. Such gastric juice, without an "extrinsic factor" such as beef or vitamin B<sub>12</sub>, when properly concentrated, gives a prompt hemopoietic response following intramuscular injection in a patient with pernicious anemia. There is no noteworthy histologic change at the site of injection in man and in rabbits (figure 1 (B)), and we believe, therefore, that an "extrinsic factor" is not essential in parenteral administration.

### METHODS OF PREPARATION

Various methods of preparing gastric juice and gastric contents for intramuscular injection have been tried. Concentration by evaporation is unsatisfactory, but (a) concentration *in vacuo* yields an active product. *Addisin* in active form has also been obtained (b) by preliminary concentration *in vacuo*, dialysis, and further concentration *in vacuo* of the dialysate; and (c) by esterification of the concentrate obtained in either of the two preceding methods. A paper giving the details of these procedures is in preparation.<sup>5</sup> As yet, we do not know which method yields the most active product. In each of the methods hy-

\*Read before the Montreal Meeting of the American College of Physicians, February 7, 1933.

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drochloric acid has been neutralized *after* concentration. Sodium hydroxide, sodium bicarbonate or a saturated solution of disodium hydrogen phosphate has been used for neutralization of the acid. Enough is added to render the mixture faintly alkaline to litmus. With

temperature of the gastric contents be kept below 37°C. in any of the procedures mentioned above.

#### DOSAGE

To establish a rough measure of dosage, we have designated as *one unit*

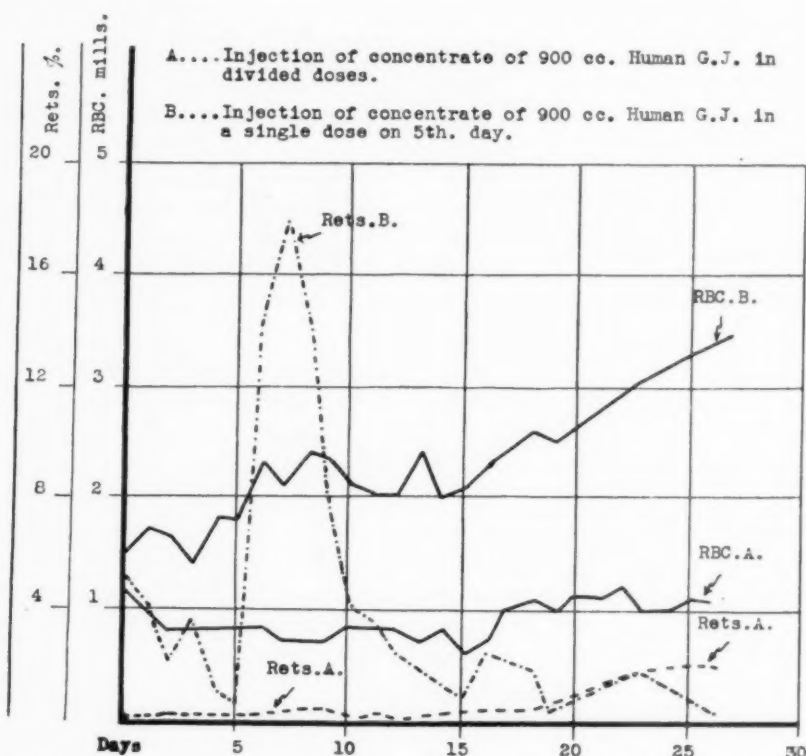


FIG. 1. A. Percentage of reticulocytes and red cell count following 9 units of human gastric juice in *divided* doses. B. The same following 9 units in a *single* dose.

aseptic precautions, the final product is usually sterile. When contaminated, however, the neutralized concentrate is diluted with four volumes of ethyl alcohol. The mixture is then passed through a Berkefeld filter, and the filtrate is collected in a sterile flask. The alcohol is readily removed by distillation *in vacuo*. It is important that the

of addisin the material recovered from 100 c.c. of original gastric juice or gastric contents. It has been found that repeated small injections are less effective than a single large dose (figure 1). Thus, the administration in divided doses of 9 units of addisin (human) has failed to produce the hematologic response in pernicious

anemia which later followed a single injection of 9 units in the same patient. Analogous results have been obtained with addisin from swine.

The hematologic response to addisin prepared by each of the three methods

shown definite evidence of hemopoietic activity.

Large quantities of gastric contents may be secured at slaughter houses from swine and cattle. Unlike the pure gastric juice obtainable from man or

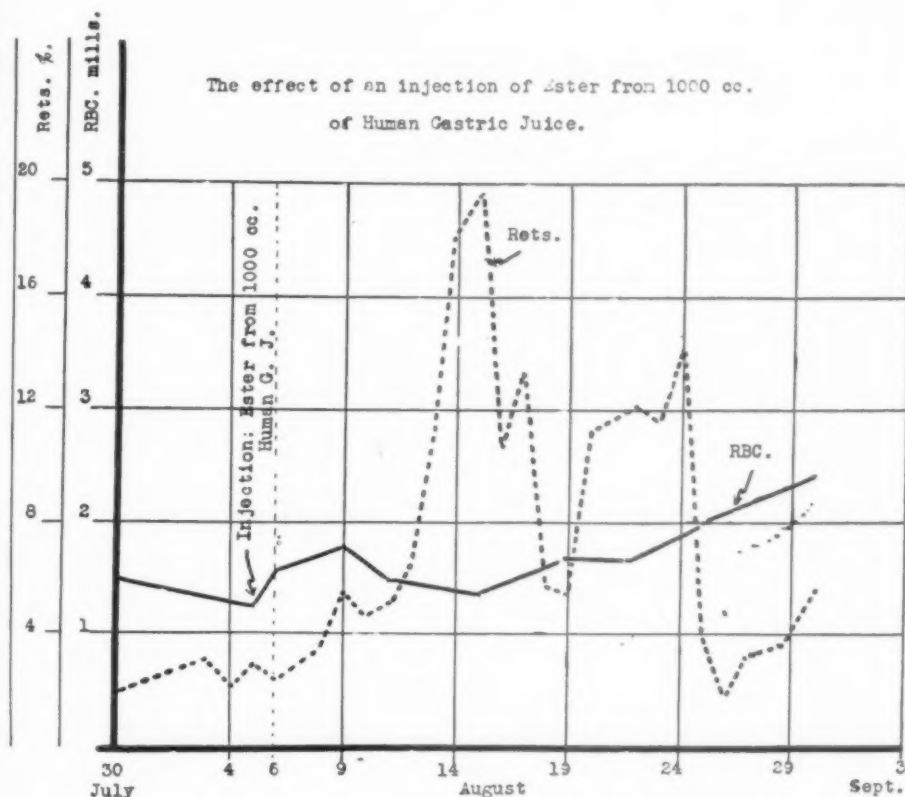


FIG. 2. Percentage of reticulocytes and red cell count following the injection of 10 units of ethyl ester of human gastric juice.

referred to previously is prompt in pernicious anemia. The product obtained by concentration *in vacuo* of human gastric juice and its ethyl ester each cause reticulocytosis and maturation of the red cells (figures 1 (B) and 2). Studies with the dialysate of concentrated human gastric juice have also

from dogs with a gastric fistula, the gastric contents of swine and cattle contain food in various stages of digestion. This material is analogous to the gastric juice plus beef or vitamin B<sub>2</sub>, as employed in Castle's experiments, but the material obtained from its concentration gives a response in

every way similar to that obtained from concentrated human gastric juice without an extrinsic factor.

#### PERNICIOUS ANEMIA

Remarkable hemopoietic responses in pernicious anemia have followed the

globin from 47 per cent to 93 per cent (figure 3). A second patient with pernicious anemia received 57 units of concentrated swine gastric contents. The immediate effect was a blood crisis lasting 24 days and a reticulocytosis of 44 days' duration. Without other

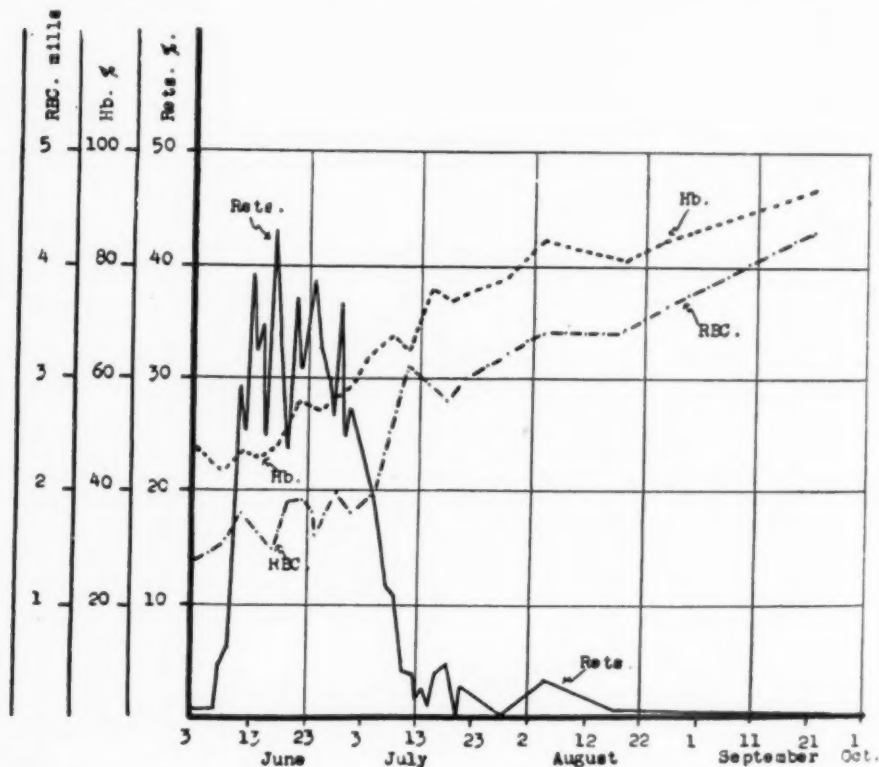


FIG. 3. The hematologic response following a single dose of 30 units of the ethyl ester of swine gastric contents.

use of single large doses of addisin obtained from swine. The injection of 30 units of esterified concentrate resulted in a prompt reticulocytosis of 24 days' duration, accompanied by a blood crisis during the first 12 days. In the course of 115 days, without further treatment, the red count rose from 1.4 million to 4.5 million and the hemo-

treatment, there was a rise in the red count from 1.5 million to 4.2 million and in hemoglobin from 44 per cent to 80 per cent in the course of 64 days (figure 4). From patients now under observation, it is probable that similar results may be expected with addisin obtained by dialysis and also from the esterified dialysate. Following intra-

muscular injection of a large dose, the greater part of the addisin may be transported to the liver for storage, though proof of this is lacking.

Studies on addisin in the gastric contents of cattle are not advanced to

the filtered gastric contents of cattle ten minutes after slaughtering. Their results are analogous to those reported by Castle<sup>3</sup> and his co-workers with oral administration of human gastric juice incubated with beef or with vitamin

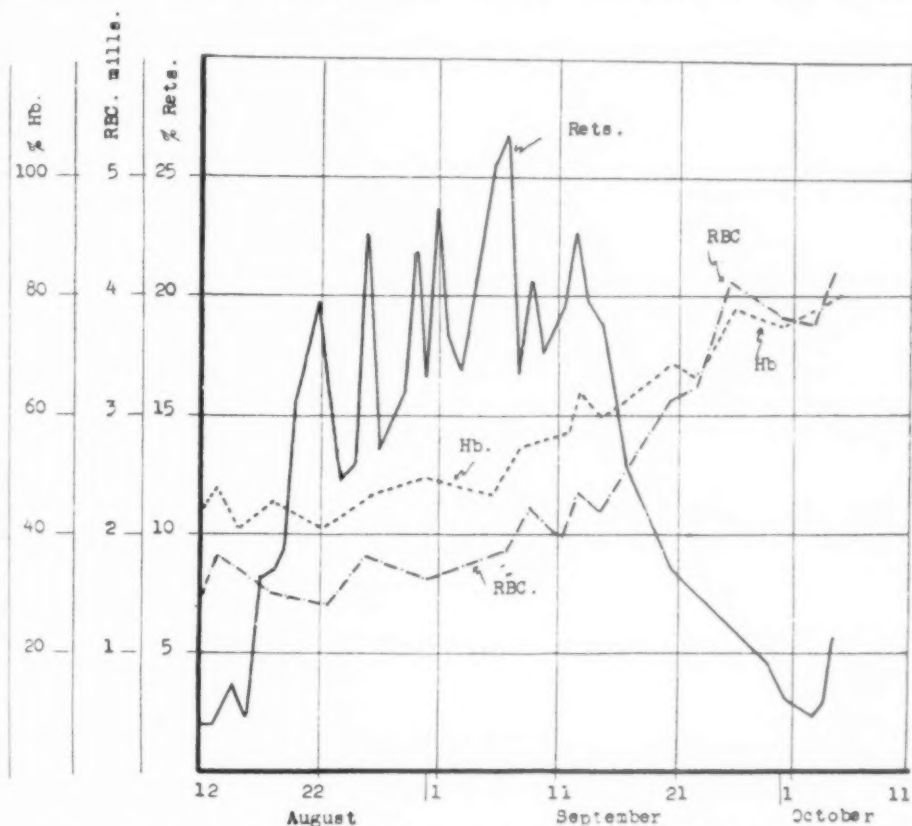


FIG. 4. The hematologic response following a single dose of 57 units of concentrated swine gastric contents.

the point we have reached with material from man and swine. There is, however, definite evidence of hemopoietic activity following intramuscular injection of the concentrate of the gastric contents of cattle. Williams and Vander Veer<sup>5</sup> have obtained a remission in pernicious anemia in four patients by the oral administration of

B<sub>2</sub>. In the light of these positive findings, it is surprising that Wilkinson<sup>6</sup> was able to obtain no response from administering preparations of the stomach tissue of cattle.

To date, five patients with pernicious anemia in relapse have received injections of concentrated human gastric juice and eleven have been given con-

centrated swine gastric contents. In each, a reticulocytosis was produced. The earliest response was within 10 hours, the latest within 5 days. In Conner's<sup>7</sup> patient, treated with human gastric juice, the reticulocytosis appeared on the tenth day. The best results, as judged by height and duration of reticulocytosis and blood crisis and by maturation of the erythrocytes, have followed the single injection of 30 to 60 units of potent material obtained by concentration *in vacuo* of swine gastric contents and by the esterified concentrate. An inadequate supply of material secured by dialysis has thus far prevented a comparison of potency with the other preparations.

Symptoms of shock, possibly due to histamine, have developed promptly on attempts to administer, intravenously, concentrated gastric contents (both from man and from swine). With our present preparations, intravenous use is dangerous and is not employed. With most of the preparations we have used, intramuscular injection has caused only a minor local reaction and little or no general reaction. Before injecting, it is important to be sure that the needle has not entered a vein. No anaphylactic phenomena have occurred.

#### ERYTHREMIA

Erythremia (polycythemia vera) is in many respects the antithesis of pernicious anemia. The etiology is unknown. In this disease there is a normoblastic marrow in contrast to the megaloblastic marrow of pernicious anemia. Theoretically, most of the changes observed in this disease might result from a hypersecretion of addi-

sin or from a hypersusceptibility of the bone marrow to stimulation.<sup>8</sup> A patient\* with 8.9 million erythrocytes was given 12.5 units of addisin (swine). The immediate response was a reticulocytosis of 2.5 per cent and 14,700 red cells per cu. mm. containing minute nuclear particles. The latter is a reaction to addisin which we have observed repeatedly in pernicious anemia at the onset of the reticulocytosis or just preceding it. In the patient's blood, none of these cells was found prior to the injection of addisin. A week later they had disappeared. A patient with pernicious anemia, refractory to liver extract intramuscularly, whose red count was 4.1 million, received 3 units of addisin (human). A reticulocytosis of 2.7 per cent and increase in red cells containing nuclear particles to 6,500 per cu. mm. appeared promptly, followed by a rise of the red count and hemoglobin to normal. The numerical response of reticulocytes of the patient with erythremia was twice that of the patient with pernicious anemia (table 1). However, differences in dosage and in preparations may account for this. The bone marrow of a second patient with erythremia showed a similar response to addisin.

It is a matter of interest that the first patient with erythremia has also had a duodenal ulcer. He has kept careful records of his blood counts over a period of years. In June 1930, when the red count was 10.0 million, he began gastric aspiration at 9:30 p. m. and lavage three to four times

\*We are indebted to Dr. D. P. Abbott of Chicago for the opportunity to study this patient.

each week and continued this until the following December. Without other treatment, there was a steady decrease in the red count to 5.3 million. The lavage was discontinued in December, and in the course of the next few months the count rose again to 10.2 million. The lavage three to four times weekly for a period

cytosis, which is permanent in acholuric jaundice, is seen temporarily in pernicious anemia in response to liver and its derivatives, to ventriculin and to addisin, and in spontaneous remissions. In pernicious anemia, the low red count is due chiefly to failure of both production and maturation of the erythrocytes. In acholuric jaundice, on

TABLE I  
MAXIMAL RETICULOCYTE RESPONSE TO ADDISIN IN REMISSION  
OF PERNICIOUS ANEMIA AND IN ERYTHREMIA

Disease	No. of red blood cells	Percentage of reticulocytes	No. of reticulocytes
Pernicious anemia	4.1 million	2.7	110,700
Erythremia	8.9 million	2.5	212,500

of six months must have removed an appreciable quantity of addisin from the stomach, a fact which we believe supports our theory and may explain the return of the blood count to a normal level. Through the action of drugs and roentgen-ray exposures over the stomach, as well as by repeated injections of histamine, we have attempted to lessen the secretion of addisin and so to improve the condition of the blood. As yet, we have not met with success.

#### ACHOLURIC JAUNDICE

Acholuric jaundice is a disease with characteristic hematologic findings. In certain respects, the qualitative blood changes are similar to those seen in pernicious anemia. The increase in the bilirubin of the serum and of urobilin in the urine in each of these diseases is generally attributed to increased destruction of the red cells. The reticulo-

the other hand, lack of normal maturation of the red cells may be an important factor in causing the anemia. Theoretically, it would seem possible that addisin might promote maturation in this disease. If so, one would expect a decrease in reticulocytes following its administration in acholuric jaundice,—a reaction the reverse of that seen in pernicious anemia.

There has been opportunity to study the effect of addisin in only one patient with acholuric jaundice. Daily reticulocyte counts for a period of two months showed a variation between 11.6 per cent and 23.1 per cent. The mean percentage for this period was 15.8. On December 19th, 30 units of addisin were given. Three days later the reticulocytes had decreased to 8.9 per cent and at the end of five days the minimum of 6.7 per cent was reached. The percentage was relatively low for the next six days (figure

5) and then rose. This lot of addisin, when given to a patient with pernicious anemia, was found to be of low potency. It caused a reticulocytosis which was maximal on the fifth day. In the patient with acholuric jaundice it may be significant that the *minimal* percentage of reticulocytes occurred also on the fifth day after the injection.

A second intragluteal injection of 55 units of this lot of addisin was given on January 20th, when the reticulocyte percentage was 11.5. On January 23rd, the percentage had decreased to 5.8 and on January 25th it was 6.6 per cent.

The decrease in reticulocytes soon after each of two doses of addisin is significant of an effect on the bone marrow and indicates the possibility of establishing better, perhaps normal, maturation in acholuric jaundice through the use of more potent preparations. Studies on the fragility of the erythrocytes and bilirubin content of the serum before and after addisin are also being made, both in pernicious anemia and acholuric jaundice.

#### AGRANULOCYTIC ANGINA

In agranulocytic angina there has also been opportunity to study the effect of addisin in one patient.\* A white male, aged 21, was admitted to the hospital January 15, 1933. There was a history of sore throat, beginning four days before admission. Two days later the temperature was 102. The throat became worse. He had one chill the night before admission, and was ex-

tremely prostrated. His temperature was 103, pulse 118, respirations 26. There were herpes on the lips and nose. Numerous superficial ulcers were seen on the gums and anterior pillars, and there was a larger ulcer on the lower half of the left tonsil. The glands at the angle of the jaw were enlarged and tender. The remainder of the physical examination was negative. Examination of the blood showed 6.7 million red cells, 115 per cent hemoglobin (Sahli), 1,400 leukocytes. A differential count showed only 7 per cent polymorphonuclear neutrophils and no other granulocytes. A diagnosis of agranulocytic angina was made.

On the evening of January 16th, the patient was given 30 units of addisin, and a remarkable leukocytic response followed, as shown in table 2. The counts were controlled with the supravital technic. In less than 24 hours there was an increase in the granulocytes, and soon myelocytes in appreciable quantity were found. Evidence of marked stimulation of the bone marrow is reflected in the differential counts and in the increase in the number of leukocytes. Rapid clinical improvement also accompanied this change in the blood. The temperature was normal at the end of two and one-half days following injection and has remained so.

Here again the result in a single case is so encouraging that an extensive trial of this form of treatment is indicated as soon as material, both clinical and therapeutic, is available.

The lack of an adequate supply of addisin of proved activity has prevented its trial in other blood diseases, such

\*This case is being reported elsewhere in greater detail.

as secondary anemia, idiopathic hypochromic anemia, sickle cell anemia, the thrombopenic purpuras, the leukemias, et cetera.

2. Addisin may be recovered in a form suitable for intramuscular injection by concentration *in vacuo*, by dialysis and by conversion to an ethyl

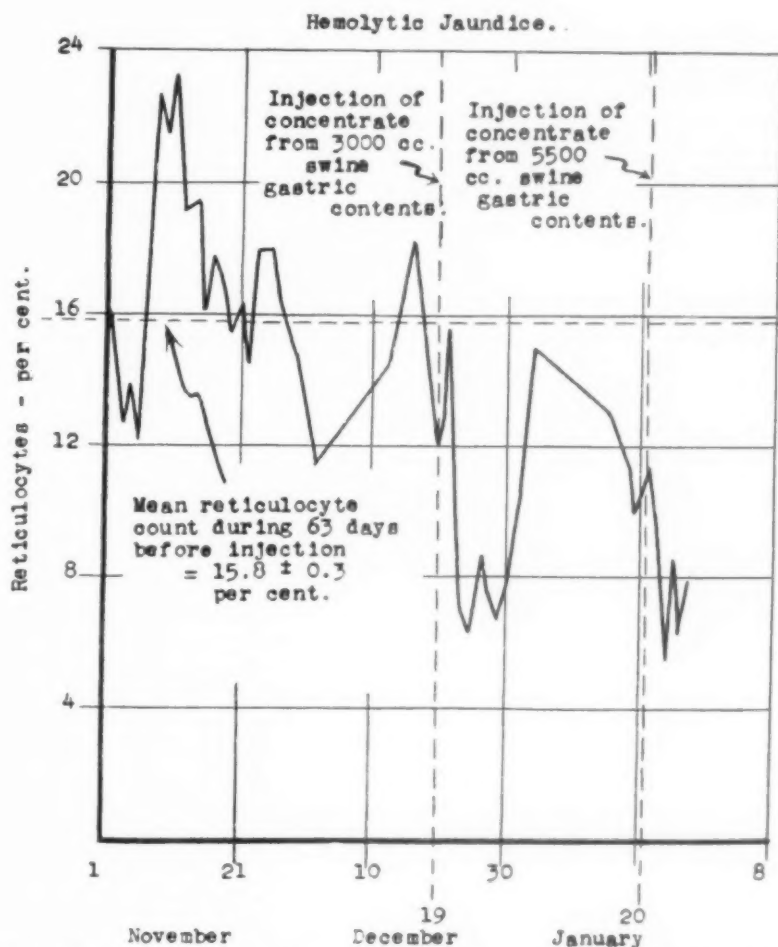


FIG. 5. The decrease in the percentage of reticulocytes following the injection of the concentrate of swine gastric contents.

### CONCLUSIONS

1. An hemopoietic hormone (addisin) is a normal constituent of the gastric secretion of man, dogs, swine and cattle. It is probably widely distributed in the animal kingdom.

ester. A preparation for intravenous use has not yet been obtained.

3. A single large dose of addisin may be sufficient to induce a remission in pernicious anemia, and is more effective than repeated small doses.

4. There is evidence to suggest that

TABLE II  
THE LEUKOCYTIC RESPONSE TO ADDISIN IN AGRANULOCYTIC ANGINA\*

Date	Leuko- cytes	Lympho- cytes	Mono- cytes	Polymorpho- nuclears	Eosino- philes	Baso- philes	Myelo- cytes	Unclassi- fied
1-16	1,400 (30 units of addisin—swine gastric contents—given 5 p.m., 1-16)	62.0	28.0	7.0	0.0	0.0	0.0	3.0
1-17	1,600	39.0	39.0	12.0	5.0	0.0	3.0	2.0
1-18	2,700	41.0	28.0	23.0	3.0	0.0	2.0	3.0
1-19	2,300	48.0 (Temperature normal since 6 a.m., 1-19)	18.0	30.0	0.0	0.0	1.0	3.0
1-20	5,700	34.0	22.0	42.0	0.0	0.0	0.5	1.5
1-21	7,400	22.5	23.0	52.0	0.0	0.0	2.5	0.0
1-23	10,900	21.5	18.5	59.5	0.0	0.0	0.5	0.0

\*The differential counts were controlled with supravital technic. The figures represent percentages. Blood for counts was taken daily in the forenoon.

the cause of erythremia may be a hypersecretion of addisin or a hypersusceptibility to stimulation by it on the part of the bone marrow.

5. The results of treatment of acholuric jaundice with addisin are sufficiently encouraging to warrant further trial. The possibility of establishing normal maturation of the red cells is suggested.

6. In a patient with agranulocytic angina, the leukocytic reaction and clinical improvement have been remarkably prompt. In this disease, it is possible that addisin may be curative.

7. Theoretical considerations indicate the possibility that addisin may play a significant rôle in other blood dyscrasias.

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## Amebic Invasion of Lymphoid Tissue and Its Probable Clinical Significance\*

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IN 1922, Ely, Reed and Wyckoff,<sup>1</sup> and Kofoid and Swezy<sup>2</sup> announced the finding of *Endameba histolytica* in the lesions of arthritis deformans. In this same year Kofoid, Boyers and Swezy<sup>3</sup> described the presence of the amebae in the lymph nodes in cases of Hodgkin's disease. A new conception of the clinical picture of chronic amebiasis was developed as a result of these findings, and is described in the papers of Boyers, Kofoid and Swezy<sup>4</sup> in 1925, and of Craig<sup>5</sup> in 1927. The former authors, especially, stressed the multiplicity of symptoms due to chronic amebiasis and felt that the patients suffer from a true systemic infection with amebae, which they believed to be present in many sites in the body not previously considered as likely to be involved. Fatiguability, defective memory, loss of energy, nervousness and headache, are ascribed to the effects of chronic amebiasis on the nervous system. Digestive symptoms which suggest disordered function or even organic disease of the stomach or liver; constipation alternating with brief periods of diarrhea; cough, with or without bloody sputum; rapid pulse; defective vision, with or without iritis,

were also included as a part of the clinical picture. According to these authors, patients with chronic amebiasis might or might not show such gross lesions as abscess of the liver, lung, brain, skin ulcers, etc., as a cause for these widespread symptoms.

To explain the presence of amebae in places outside the colon, as, for instance, the liver, lungs, brain, spleen, bone marrow and lymph nodes, the conception of "systemic infection" had been previously offered by Kofoid, Boyers and Swezy,<sup>6</sup> who asserted that: "From its portal of entry through the epithelium of the colon into the submucosa, *Endameba dysenteriae* tends to spread in the margins of ulcers of the colon into capillaries and smaller veins, and thence may make its way into the capillary net of the liver, through the heart to the capillary net of the lung, and thence into the systemic circulation." This new conception of chronic amebiasis stimulated a new interest in these diseases and led to more detailed pathological studies of amebic lesions, the findings of which have been published in papers during the past several years.

The present paper will present an account of the pathology of amebic lesions resulting from researches on the cultivation of *Endameba histolytica*

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in kittens in 1924 and 1925,<sup>7</sup> and also notes of certain other studies carried out in collaboration with Dr. C. E. Forkner in Boston on a number of persons with Hodgkin's disease. The latter work was supervised by Dr. George R. Minot, of the Collis P. Huntington Memorial Hospital, and by the late Dr. Francis W. Peabody, director of the Thorndike Memorial Laboratory of the Boston City Hospital. In the discussion it will be shown that the results of these studies may provide a pathological basis for the clinical concept of chronic amebiasis.

#### **PATHOLOGY OF AMEBIC LESIONS**

Prior to the year 1891, much confusion existed among pathologists concerning the lesions found at autopsy in the so-called "follicular form" and in the "diphtheritic form" of dysenteries. In 1891, Councilman and Lafleur<sup>8</sup> first accurately described the pathology of amebic lesions and established the differentiation between colitis of amebic origin and that of bacterial origin. By extensive review of the literature they showed that many of the cases of "follicular" and "diphtheritic" colitis, as previously described by American, English, French and German physicians in the tropical countries, were probably instances of amebic infection.

The work of Councilman and Lafleur was confirmed and amplified by that of other investigators, Rogers,<sup>9</sup> Kuenen,<sup>10</sup> Viereck,<sup>11</sup> and Woolley and Musgrave.<sup>12</sup> More recent investigators have studied the lesions in the intestines and liver of kittens experimentally infected with these parasitic amebae. Their studies revealed the identity of

the gross and microscopic amebic lesions in kittens with those in man. Furthermore, the finer pathological details of the very early lesions of amebiasis were more clearly described. We now know, as a result of these later studies by Dopter,<sup>13</sup> Jürgens,<sup>14</sup> Wenyon,<sup>15</sup> Dale and Dobell,<sup>16</sup> Sellards and Theiler,<sup>17</sup> Boeck and Drbohlav,<sup>7</sup> Rees,<sup>18</sup> and Martin,<sup>19</sup> that in experimental amebiasis in kittens, as in human amebiasis, there occurs not only an erosion-ulceration of the mucosa, often with the formation of a diphtheritic membrane, that may later invade the deeper coats of the colon, appendix and terminal ileum, but also invasion and destruction of solitary lymph follicles. We shall now briefly consider the microscopic appearance of the intestinal lesions found in amebiasis.

*Intestinal Lesions.* In stained sections of tissues of the colon, amebae may be found upon the surface of the epithelium (figure 1) and less frequently in the glandular crypts. They appear to secrete a toxic and proteolytic substance or substances that cause a cytolytic and liquefying necrosis of the tissues they invade. They first produce an erosion-lesion of the surface epithelium and sometimes form, with the aid of a secondary bacterial invasion, a diphtheritic membrane composed of fibrin, mucus, cellular remains, bacteria, and amebae (figure 1). This membrane was noted in the early observations of Finger (1849), Lyons (1856), Parkes (1860), Woodward (1880), and Maclean (1886), cited by Councilman and Lafleur.<sup>8</sup>

Following the destruction of the epithelium by the formation of erosion-ulcers, the amebae may continue to de-

stroy simultaneously both the interstitial tissue of the tunica propria and the epithelial covering of the glands. They may often, however, be seen passing into and down the lymphatic channels of the tunica propria into larger lymphatics in the submucosa. There they seem to be arrested in their progress,

bacterial invasion of variable amount may occur in many of the larger ulcers and the deeper erosion-ulcer lesions. The results of this complication are marked polymorphonuclear infiltration and a purulent exudate.

*Liver, Lung and Brain Abscesses.* With the formation of deep ulcers in



FIG. 1. Erosion-ulceration by amebae, with formation of diphtheritic membrane.  $\times 150$ .

creating a localized area of necrosis and forming abscesses. As this area grows the overlying mucosa may slough with the production of a large deep ulcer (figure 2). The amebae in the bottom of the glands cause necrosis of the adjacent epithelial cells of the crypt and invade the mucosa above the muscularis mucosae; later a larger ulcer develops from the sloughing of the mucosa above the lesion. Secondary

the submucosa, the amebae may find their way into the blood capillaries and may thus be carried by the portal circulation to the liver. Here, in some cases, a hepatitis occurs which may progress, by proteolytic and liquefying necrosis of the liver parenchyma, and result in single or multiple amebic abscesses. A pulmonary abscess may be produced from this focus in the liver most frequently by direct extension

through the diaphragm and occasionally by blood stream invasion. In rare cases further blood stream invasion has caused an embolic brain abscess or an abscess of the spleen. These instances, however, have nearly always been associated with an older abscess of either the liver or lung and gen-

tissues are also important because of their probable relationship to the symptoms present in cases of chronic amebiasis.

*Lesions in Lymph Follicles.* Opportunities of observing several progressive stages in the early invasion, as well as the gradual and ultimate de-

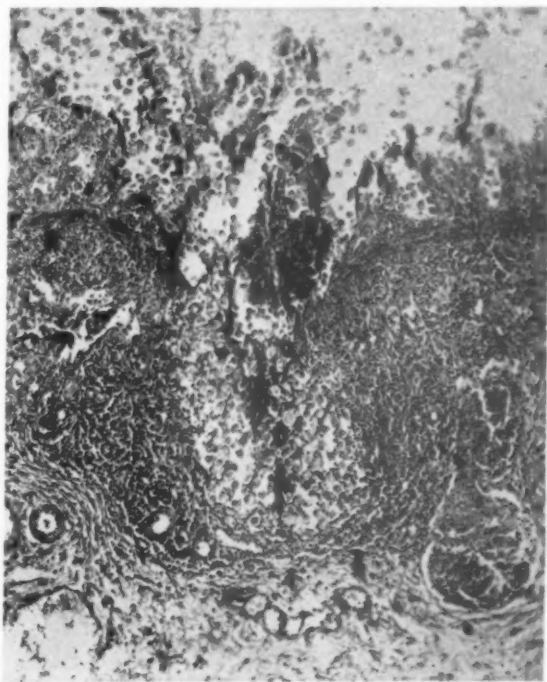


FIG. 2. Deep submucosal amebic ulcer with complete destruction of intestinal mucosa. x 75.

erally with a previous amebic colitis. This, in a general way, characterizes the manner and progress of amebic infection in the intestine, liver and lungs, with the exception of lesions in the lymphoid tissues. The pathology of the lesions in lymphoid tissues has not been studied as extensively as that of the ulcerative lesions of the intestine, although lesions in the lymphoid

struction of the lymph follicles, were afforded by lesions occurring in Peyer's patches of the terminal ileum of five kittens experimentally infected with *Endameba histolytica*. The amebae showed an apparent selective action in attacking the follicles, as was evident from an initial necrosis of the epithelium covering the tip of the solitary follicle. The adjacent epithelium

of the intestinal mucus glands was not affected (figures 3 and 4). Following the destruction of the epithelium over the follicle, the amebae moved down into the body of the follicle, and a sinus tract was formed. The lymphoid cells of the follicle and the interstitial cells

tered polymorphonuclears, large mononuclear cells, and a proliferation of connective tissue elements, attempting to wall off the lesion. In the center of the gland there was progressive destruction of the lymph cells by the amebae, resulting in much cellular de-



FIG. 3. Very early amebic abscess in solitary follicle, with destruction of epithelium over tip of the follicle, and downward migration of amebae—adjacent epithelium normal. x 100.

of the reticulum underwent necrosis, the nuclei becoming pyknotic and the cytoplasm undergoing gradual dissolution or liquefaction (figure 5). There was practically no evidence of any cellular reaction to the infection in the early stages of the invasion, but later stages showed an infiltration of the submucosa at the outer limits of each follicle, with plasma cells chiefly, scat-

tritus. The amebae, as they multiplied and formed a localized abscess, appeared as large cells within a nest of lymphoid cells (figures 6 and 7). The abscess thus produced continued to grow until the whole follicle was destroyed. Later, the mucosa overlying the abscess in the submucosa may, in some cases, slough off and produce a large deep ulcer (figure 8). There

was no evidence of bacterial invasion of the follicles in the early stages of the amebic invasion.

The follicles in the colon also showed early invasion by amebae. This condition, too, was noted by pathologists studying lesions from the human colon. Such an invasion of lymphoid tissue

lymphoid follicles of the colon and terminal ileum in human cases. Although these early investigators felt that the disease often began in these structures, Councilman and Lafleur considered the amebic invasion of the follicles a passive action. Somewhat later Kuenen<sup>10</sup> reported the death of a

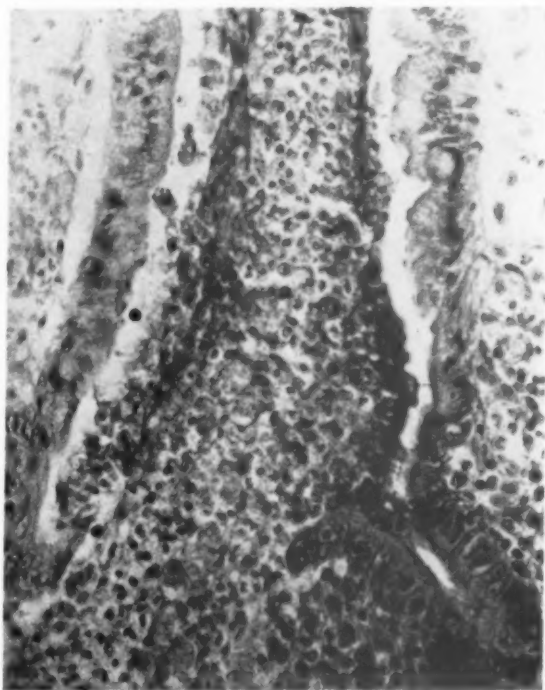


FIG. 4. Same as figure 3, except higher magnification, to show amebae in lymph follicle and normal adjacent epithelium.  $\times 200$ .

may, however, go on simultaneously with the erosion destruction of the mucosa adjacent to the follicle or elsewhere, depending upon the location of the amebic invasion (figure 9).

The observations of Lyons (1856), Parkes (1860), Woodward (1880), and Maclean (1886), cited by Councilman and Lafleur, also showed abscesses or ulcers occurring first in the

patient due to peritonitis from a perforation of the ileum by amebae invading a Peyer's patch. This same patient also had typhoid fever, so the cause of the perforation may have been of typhoid origin, the amebae being present in the lesion and passing through into the abdomen. Very recently Hegner, Johnson and Stabler<sup>20</sup> reported amebic invasion of lymph follicles in

an appendix removed at operation from a patient in whose stools *Endameba histolytica* had been previously found.

The very recent studies made by various investigators of lesions of the lymphoid follicles occurring in kittens and monkeys experimentally infected

vessels and produce submucous abscesses in the follicles." He felt that the follicular abscesses were of bacterial origin, amebae wandering into and around them after death of the kitten. Hegner, Johnson and Stabler, who studied experimental amebic lesions in monkeys, were of the opinion

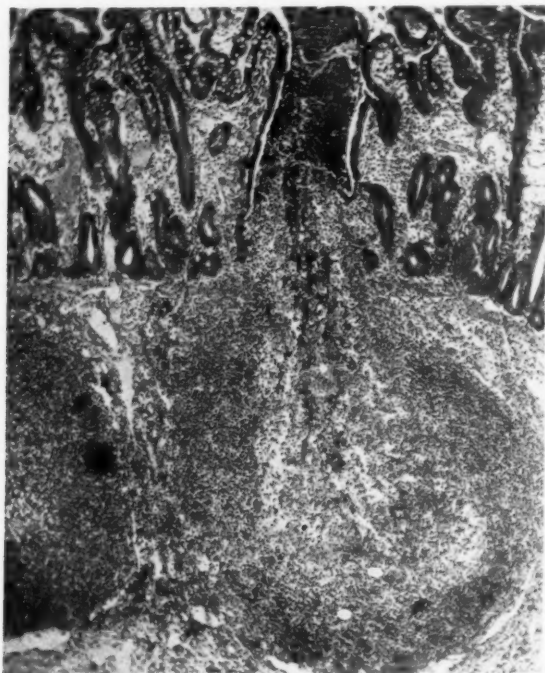


FIG. 5. Amebic abscess in lymph follicle, showing sinus tract to lumen of intestine—no ulceration of adjacent epithelium.  $\times 50$ .

with *Endameba histolytica* are not in agreement as to whether such lesions should be attributed to amebic or to bacterial action.

Hiyeda<sup>21</sup> found no amebae in follicular ulcers, and thought that the lesions were due to bacterial invasion. Ratcliffe<sup>22</sup> believed that: "The apparent rôle of the amebae is superficial destruction of the mucosa which allows pyogenic bacteria to invade the lymph

that the follicular abscesses were of bacterial origin because they found no amebae in them. On the other hand, Dopter, Jürgens, Martin and the author have recorded observations in which the amebae were found in the abscesses of the lymph follicles. We may conclude, therefore, that follicular abscesses may be of either bacterial or amebic origin. Abscesses of both types may occur in the same subject. Of



FIG. 6. Peyer's Patch, frontal section, showing nest of amebae in each follicle.  $\times 30$ .

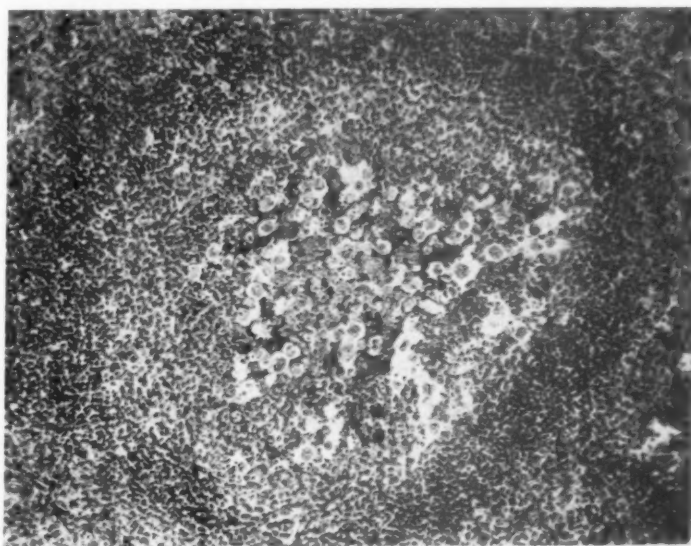


FIG. 7. Amebic follicular abscess, from figure 6, higher magnification.  $\times 75$ .

such a nature were some of the cases reported in early writings on "follicular" colitis. It may be that the very early lesions as reported by Jürgens and the author were not observed by Hiyeda, Ratcliffe, nor by Hegner and his associates.

writer's observations and those of Jürgens indicate that these glands are very early attacked by the amebae, even before the adjacent epithelium is damaged, and long before there is any evidence of bacterial invasion such as Ratcliffe maintained. It is also signifi-



FIG. 8. Large sloughing follicular abscess. x 75.

Jürgens was the earliest investigator to note that in kittens the amebae seemed to invade the lymph follicles first while the adjacent intestinal epithelium remained intact and apparently healthy. Although Martin also observed amebic abscesses in the follicles, he did not feel that these structures were predisposed to the attack of *Endameba histolytica*. He did not, however, observe early stages in the invasion of these glands. The present

cant that the appendiceal infection with *Endameba histolytica*, reported by Hegner, Johnson and Stabler, showed, as the only evidence of microscopic damage, two small early amebic ulcers in the lymph follicles.

To summarize, the pathology of amebic lesions indicates that there are two distinct, fundamental lesions produced by these parasites; first, an early erosion-ulcer which is the result of the invasion and destruction of epithelial

tissue of the intestine (this is also true when other epithelial structures are attacked); second, an abscess which is produced in solitary lymph follicles, the liver, lung, brain and spleen. There is considerable pathological evidence

These glands contained certain cells which were interpreted as *Endameba histolytica* by the authors. Later they reported that amebae were found in the stools of 18 out of 20 cases of Hodgkin's disease studied by them.



FIG. 9. Solitary follicular amebic abscess, with erosion-ulceration and diphtheritic membrane above.  $\times 75$ .

that the amebae may attack the lymph follicles of the colon, appendix and terminal ileum before producing much or any damage to the adjacent epithelium.

#### AMEBIASIS AND HODGKIN'S DISEASE

Kofoed, Boyers and Swezy,<sup>3</sup> in 1922, reported on several cases of Hodgkin's disease confirmed by pathological examination of excised lymph glands.

Dr. C. L. Forkner and the author, while in Boston, studied a number of cases of Hodgkin's disease from two aspects. Dr. Forkner was interested in the diagnosis of diseases, such as Hodgkin's and malignancy, by glandular puncture. The affected glands were punctured with a needle in the lumen of which was a coarse dental broach. The rotation of this broach and its subsequent withdrawal brought away cellular material which could then be

stained with supravital dyes and studied in the warm chamber. The report of this part of the study has been published by Dr. Forkner.<sup>23,24</sup>

The author's part in this investigation was the search for *Endameba histolytica* in the lymph node material. Culture media were inoculated to grow any amebae that might be present; and hematoxylin-stained smears were studied microscopically. The stools from many of these patients were also examined for *Endameba histolytica*. Some of the cases studied were not, however, included in the published reports of Dr. Forkner.

All the cases studied had had definite pathological diagnoses which, with few exceptions, coincided with the results obtained from gland puncture. The author collaborated in a study of fifteen cases of lymphoblastoma, of which nine were diagnosed as Hodgkin's disease; three as lymphoblastoma of the rapidly growing type; and two as lymphoblastoma of the leukemic type. In none of the cases of lymphoblastoma reported by Forkner, nor in any of the additional cases studied and not reported, was *Endameba histolytica* ever observed either among the living cells stained with vital dyes, or in the stained pathological sections of the glands. Biopsy material obtained from the nine cases of Hodgkin's disease was inoculated in culture media, but these cultures also proved negative for amebae.

The stool examinations of these patients revealed that *Endameba histolytica* was present in the stools of but one of these cases. *Endameba coli* was also present in this case. Of the remaining eight cases, *Endameba coli* occurred in one case, *Endolimax nana* in one case, and *Giardia lamblia* in one

case; the other five cases were negative for intestinal protozoa. Three stool examinations were made in one of these cases; and six stool examinations in each of the other eight cases. The results of the stool examinations were in marked contrast with those obtained by Kofoid, Boyers and Swezy<sup>6</sup> who found *Endameba histolytica* in the stools of eighteen out of twenty patients having Hodgkin's disease.

To summarize this investigation of the nine cases of Hodgkin's disease: amebae were absent in the stained pathological sections, in the living cells obtained by gland puncture, in this same cellular material stained with hematoxylin, and in culture media inoculated with this cellular material.

#### DISCUSSION

The clinical concept of chronic amebiasis held by Boyers, Kofoid and Swezy and others has not, for several reasons, met with general acceptance by physicians and pathologists. Their attempt to ascribe an etiological rôle to chronic amebiasis in symptom complexes characteristic of what is usually termed neurasthenia, and in such disease processes as iritis, neuritis, arthritis deformans and Hodgkin's disease could only be justified by proof of the presence of *Endameba histolytica* in the tissues of such cases.

Pathologists have failed to identify any of the cells in lesions of arthritis deformans as identical with *Endameba histolytica*. Likewise, the progressive pathology of these destructive lesions of bone is not in any way suggestive of amebic invasion, since no liquefying necrosis occurs with local abscess formation, such as is found in amebae-infested tissues. Further, the forma-

tion of bony lipping and spurs is not consistent with amebic pathology.

The presence of amebae in the enlarged lymph nodes of Hodgkin's disease has not been confirmed by other pathologists who have made a careful study of this disease. The author's investigations, as well as those of Jürgens, Martin and others, have shown that when amebae invade lymphoid follicles abscess formation results and that in such lesions amebae are easily detected. Abscess formation is very unusual in the lymph glands of Hodgkin's disease if it occurs at all. Moreover the cells in Hodgkin's glands, which Kofoed, Boyers and Swezy believed to be amebae, were difficult to find. The author's investigations on nine cases of Hodgkin's disease, together with those of Forkner and more recently those of Twort<sup>25</sup> in 1930, covering 61 cases of Hodgkin's disease, have failed to show that *Endameba histolytica* is present in the enlarged glands or in cultures inoculated with material from these glands.

All previous investigators have found little evidence of generalized systemic invasion with *Endameba histolytica*. Liver abscess, it is true, has for about 40 years been assumed to be due to ameba reaching the liver through the blood stream. However, even in India where this complication is most frequently seen, it occurs in only 20 per cent of the cases of amebic colitis. The liver is usually an efficient filter which prevents amebae from entering the blood stream. The fact that even a small amount of bile in cultures is fatal to amebae may account in part for the effective defensive rôle of the liver. Councilman and Lafleur,<sup>8</sup> Manson-Bahr,<sup>26</sup> Clark<sup>27</sup> and others have shown

that when lung abscess occurs it is more usually as a result of direct extension from a liver abscess than by invasion of the lung by amebae carried in the circulating blood. Amebic abscesses of the brain, spleen and kidneys, which are evidence of invasion of the systemic circulation, are quite rare. Therefore, to assume that systemic amebic invasion occurs with such frequency as to be accountable for such relatively common diseases as arthritis deformans, Hodgkin's disease, iritis, etc. is contrary to all previous knowledge of the pathology of the disease.

Because, then, of the lack of confirmation of their findings and because of the inherent improbability of their conception of systemic invasion, physicians and pathologists generally have not accepted the views of Boyers, Kofoed, and Swezy.

Another conception of the relationship of general constitutional conditions to chronic amebiasis was brought forward by Barrow. He first suggested that chronic amebiasis and arthritis may be related, as Ely, Reed and Wyckoff later stated, but he held that the relationship was due to the probable presence of small lesions in the intestine that permitted the absorption of toxins, and not to the presence of amebae in the bone marrow in cases of arthritis deformans.

This particular conception of chronic amebiasis finds a definite pathological basis in the studies of the lesions of the solitary lymph follicles. All infections of *Endameba histolytica* must be considered potentially dangerous to health even in the so-called carrier cases of chronic amebiasis, as has been known for a long time. For the reasons given above, it is hardly probable

that in such chronic cases the amebae reach the bone marrow or lymph glands. They may, however, cause slight erosion-lesions of the intestinal mucosa, and may invade the solitary lymph follicles, causing abscesses such as have been previously described. These small lesions, which would not be detectable in the sigmoidoscope, represent definite portals of entry into the lymphatic system for the absorption of toxins from the colon. Hence each lesion is a focus of infection. The toxins may be liberated either by the amebae, or by the bacteria in these lesions. The toxins from the bacteria may be the more important etiological factors in the production of inferior health and chronic disease in individuals infested with *Endameba histolytica*.

The clinical application of these pathological observations is clear and indicates that all patients who are in poor health and underweight, those with nervous and physical exhaustion, and those who may be subject to recurrent attacks of arthritis and other diseases for which focal infections are

believed to be partly responsible, should be thoroughly examined for *Endameba histolytica*, just as they are examined for infected tonsils, abscessed teeth and other foci. If an amebic infection is discovered it should be eradicated by thorough treatment. Too much in the general improvement of the patient should not be expected, in view of the fact that there are most likely multiple factors at work.

To summarize, it has been shown that there are two fundamental kinds of amebic lesions: first, erosion-ulcers of the epithelium which may become deep and undermining in character, often secondarily invaded by bacteria; second, a localized abscess in lymph follicles, liver, lung, brain and spleen. Further investigations on cases of Hodgkin's disease have failed to show any amebae present in the enlarged lymph nodes. It is suggested that the small erosion-ulcers of the epithelium, and especially the localized abscesses seen in the solitary lymph follicles, provide a pathological basis for the clinical conception of chronic amebiasis.

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## Variations in the Volume and in the Acid Content of Gastric Secretion of Normal Individuals Following Stimulation by Histamine\*†

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**D**URING the last few years the analysis of gastric contents obtained after stimulation by histamine has come into general use.

The work of Bloomfield and Poland<sup>1,2</sup> on the acidity of gastric juice following histamine stimulation has shown that the volume and acidity rapidly increase, the maximum being reached in 20 to 30 minutes after injection, after which time the volumes diminish, while the acidity maintains its high level throughout the test of an hour's duration. They found a constancy of response of volume and acid after giving repeated doses of the same amount of histamine to a given individual.

Gompertz and Cohen<sup>3</sup> have shown that as little as 0.25 mg. of histamine hydrochloride will give a gastric secretory response, and that in using larger doses (0.5 mg., 0.75 mg., 1.0 mg.) a greater response is usually obtained, but that the results are not mathematically proportional to the size of the dose.

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Kinsella,<sup>4</sup> after reviewing the literature concerning the acidity at the cardiac and pyloric ends of the stomach, reports that he finds the gastric contents usually more acid at the cardiac than at the pyloric end if saliva is excluded.

The gastric secretion after stimulation by histamine has been studied in two healthy men aged 28 and 32 years. In aspirating the gastric secretion the Rehfuess tube was used, the 60 cm. mark being kept at the incisor teeth. Continuous aspiration of the gastric secretion was performed at a negative pressure of 15 to 20 cm. of mercury, maintained by a water driven suction pump. A 15 minute fasting sample (fasting contents and any gastric secretion over 15 minutes' time) was obtained; then histamine (ergamine phosphate) was administered subcutaneously, 0.1 mg. per 10 kilograms of body weight, and the subsequent gastric secretion obtained was divided into six 10 minute samples. The volume of each sample was measured, and free and total acidity of each sample was determined using dimethylamino-azobenzol (Topfer's reagent) and phenolphthalein as indicators, the acidity being expressed in terms of 0.1 normal

acid per 100 c.c. of gastric juice. The study was carried on over a period of eight months, 16 analyses being done on one subject and seven on the other. In each of the charts the solid lines indicate the response to 0.1 mg. histamine per 10 kilograms of body weight; the broken lines to half this dose; and the dotted lines to one-fourth the first mentioned dose. All of the analyses were done by the same two individuals, thereby tending to minimize errors due to variations of technic.

Charts 1, 2, and 3 on subject F. E. show: (1) that the maximum acidity and the maximum volume per 10 minute period were always reached in the 10 to 20 minute or in the 20 to 30 minute samples, usually in the former; (2) that after the maximum acid secretion is reached, the acid rapidly diminishes, tending to approach the fasting level at the end of an hour after the administration of histamine, while there is less diminution noted in the amount of secretion per 10 minute period; (3) that a close relationship exists between the free and total acid;

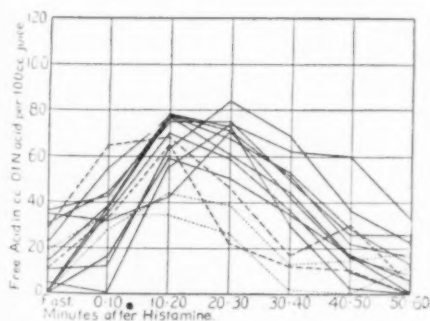


CHART I. F. E. Free Acidity Curves.  
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.  
Broken lines = 0.05 mg. histamine per 10 kilograms body weight.  
Dotted lines = 0.025 mg. histamine per 10 kilograms body weight.

(4) the maximum free acid varied from 58 to 86, the maximum total acid varied from 75 to 96, and the maxi-

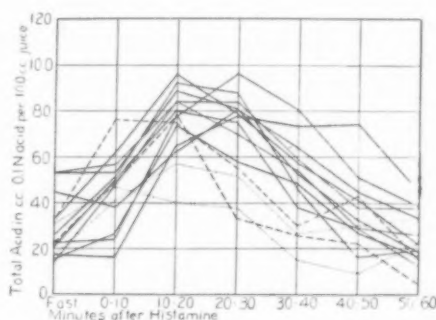


CHART II. F. E. Total Acidity Curves.  
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.  
Broken lines = 0.05 mg. histamine per 10 kilograms body weight.  
Dotted lines = 0.025 mg. histamine per 10 kilograms body weight.

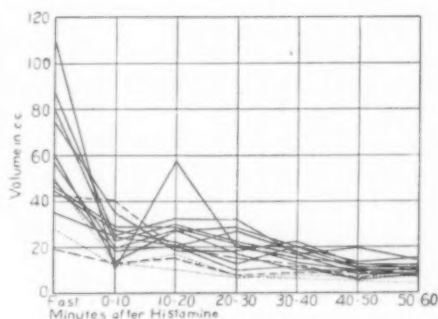


CHART III. F. E. Volume Curves.  
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.  
Broken lines = 0.05 mg. histamine per 10 kilograms body weight.  
Dotted lines = 0.025 mg. histamine per 10 kilograms body weight.

imum volume for the 10 minute period varied from 21 to 33 c.c. except on one occasion when 56 c.c. were obtained; (5) one-half of the dose of histamine gave less volume of secretion but nearly as high an acid level as the full dose; (6) one-fourth of the dose of hista-

mine did not elicit the average full dose response in either volume or acid.

Charts 4, 5, and 6 on subject C.L.B. show (1) that the maximum acidity and the maximum volume per 10 min-

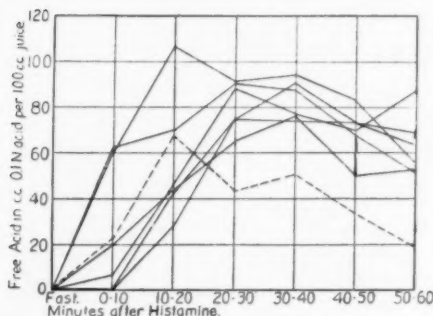


CHART IV. C. L. B. Free Acidity Curves.  
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.  
Broken line = 0.05 mg. histamine per 10 kilograms body weight.

ute period were always obtained by the end of 40 minutes after the injection of histamine, usually in the 20 to 30 minute or in the 30 to 40 minute samples; (2) that after the maximum acid secretion and the maximum volume per 10 minute period were reached there

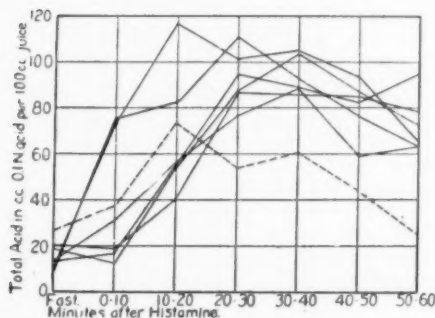


CHART V. C. L. B. Total Acidity Curves.  
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.  
Broken line = 0.05 mg. histamine per 10 kilograms body weight.

was a tendency for both acid and volume to diminish but not as rapidly as in subject F. E.; (3) that a close relationship exists between the free and total acid; (4) the maximum free acid varied from 75 to 106, the maximum total acid varied from 87 to 113, and the maximum volume per 10 minute period varied from 42 to 84 c.c.; (5) one-half of the dose of histamine did not elicit the average full dose response in either volume or acid.

Since continuous aspiration removes practically the entire secretion of the stomach it is possible to obtain from the results of these tests a quantitative measure of gastric secretory function. The influence of regurgitation of duodenal contents was probably of no significance in these tests since none of the samples was stained with bile. The amount of free or total acid, expressed as 0.1 normal acid, secreted during the hour test period is calculated in the following manner: the volume in c.c. of each 10 minute sample is multiplied by the amount of acid, in terms of 0.1 normal acid, per c.c. of that juice, and the sum of the values of each of the

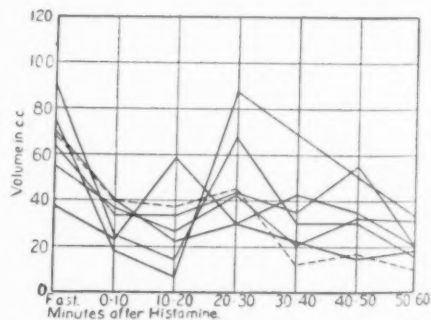


CHART VI. C. L. B. Volume Curves.  
Solid lines = 0.10 mg. histamine per 10 kilograms body weight.  
Broken line = 0.05 mg. histamine per 10 kilograms body weight.

six samples gives the total acid secretion for the hour. Table 1 shows the volume and the quantity of free and total acid secretion in the hour following stimulation by histamine. A considerable variation of acid secretion in the same individual given the same dose of histamine on different days is shown by these figures.

samples usually had the greater free and total acidity. We believe that this experiment indicates that the tube at 60 cm. removes practically all of the gastric secretion and that the secretion obtained from the cardiac end of the stomach usually has a greater acidity than that removed from the pyloric end.

TABLE I

Subject	Date 1931	Histamine in Mg. per 10 Kilograms of Body Weight	Gastric Secretion Obtained in the Hour Following Histamine Stimulation		
			Volume in c.c.	Free acid as c.c. 0.1 N. acid	Total acid as c.c. 0.1 N. acid
F.E.	4-15	0.1	100	55	66
F.E.	4-20	0.1	140	70	82
F.E.	4-22	0.1	110	42	54
F.E.	4-27	0.1	107	61	71
F.E.	4-29	0.1	126	50	68
F.E.	5- 8	0.1	122	66	78
F.E.	5-11	0.1	110	37	53
F.E.	5-13	0.1	109	51	64
F.E.	5-18	0.1	81	39	49
F.E.	5-20	0.1	92	55	64
F.E.	11-20	0.05	104	49	61
F.E.	11-23	0.025	51	17	23
F.E.	11-27	0.025	56	13	19
F.E.	11-30	0.05	62	18	25
C.L.B.	4-13	0.1	219	138	159
C.L.B.	4-22	0.1	165	119	143
C.L.B.	4-24	0.1	189	153	174
C.L.B.	5-11	0.1	195	127	152
C.L.B.	5-20	0.1	188	105	123
C.L.B.	11-23	0.1	181	96	113
C.L.B.	11-25	0.05	160	65	83

Table 2 shows the results on subject F. E. when two Rehffuss tubes were used at the same time with simultaneous and continuous aspiration, the tip of one being 60 cm. and the other 72 cm. from the incisor teeth, these tube tips being found by X-ray examination to be in the cardiac and pyloric ends of the stomach respectively. It will be noted that almost all of the secretion was obtained from the tube in the cardiac end of the stomach and that these

Our studies show less constancy in both volume and acid secretion in the same individual after repeated doses of the same amount of histamine than was found by Bloomfield and Polland. The gastric contents were usually more acid at the cardiac than at the pyloric end of the stomach. Smaller doses of histamine, while they elicit some gastric secretion, do not seem to be as satisfactory as a dose of 0.1 mg. per 10 kilograms of body weight.

TABLE II  
ANALYSIS OF GASTRIC CONTENTS OF F.E. USING 2 REHFUSS TUBES, TIPS 60 AND 72 CM.  
FROM INCISOR TEETH, 0.1 MG. HISTAMINE PER 10 KILOGRAMS BODY WEIGHT

Specimen	60 cm. tube			72 cm. tube		
	Volume in c.c.	Free acid	Total acid	Volume in c.c.	Free acid	Total acid
15' fasting	80	0	19	10	0	16
0'-10' after hist.	12	28	47	2	0	18
10'-20' " "	18	63	75	4	37	44
20'-30' " "	13	61	73	1	42	55
30'-40' " "	11	28	40	0	—	—
40'-50' " "	8	12	26	1	35	58
50'-60' " "	7	5	23	3	4	23

Specimen	60 cm. tube			72 cm. tube		
	Volume in c.c.	Free acid	Total acid	Volume in c.c.	Free acid	Total acid
15' fasting	24	14	23	7	5	17
0'-10' after hist.	20	21	33	3	10	19
10'-20' " "	30	70	86	1	33	47
20'-30' " "	11	58	67	5	44	58
30'-40' " "	8	26	40	1	25	42
40'-50' " "	8	2	18	2	21	37
50'-60' " "	11	2	16	6	0	14

## SUMMARY

1. A study of the variations in the volume and acid content of gastric secretion of two normal individuals, following stimulation by histamine (ergamine phosphate), is presented.

2. A maximum in volume and in acidity of the gastric secretion is obtained, on the average, about 30 minutes after the administration of histamine.

3. There are distinct variations in the volume and in the acidity of the gastric secretion of the same individual given the same amount of histamine on different days.

4. When gastric secretion is removed from the pyloric and cardiac ends of the stomach at the same time, the acid content of the secretion obtained at the cardiac end is usually greater.

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## Orthostatic Albuminuria

### A Comparison with Other Types of Albuminuria\*†

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**A**FTER rather completely reviewing the extensive literature of the last twenty years on orthostatic albuminuria, it is apparent that many clinical impressions have been accepted as fact without proper critical study. Few authors have presented sufficient data on carefully studied series of cases to lend weight to their conclusions.

In an effort to obtain some accurate information about orthostatic albuminuria, its effect on the patient's health, the relation it bears to glomerulonephritis, the type of patient affected, and if possible its etiology, the records of 185 patients seen at The Mayo Clinic over a period of approximately ten years were carefully analyzed. The results were tabulated at length, and the tables made are summarized in table 1. The cases studied have been divided into four groups: (1) orthostatic albuminuria; (2) albuminuria with an orthostatic response; (3) latent glomerulonephritis, and (4) chronic glomerulonephritis.

The diagnostic criteria for inclusion of cases in the first group have been the occurrence of albumin in the urine when the patient was in the erect posi-

tion, whereas a specimen excreted while the patient was lying down, or the night specimen, must have been entirely free from even traces of albumin by the usual method of detection. It is possible that this rule has excluded certain cases of orthostatic albuminuria from our first group, since, in genuine cases of this sort, the albuminuria has been demonstrated to persist a short time after the patient has lain down. The sediment in such cases is usually free from erythrocytes and casts, but it should be remembered that occasional erythrocytes or granular casts may be found in normal urine. There must have been no history suggestive of nephritis or nephrosis, nor any of the physical signs which are commonly associated with nephritis, such as changes in the vascular system, including retinitis. A slight to moderate degree of anemia, without evidence of renal or vascular disease, was considered permissible. The criteria for a diagnosis of albuminuria with an orthostatic response have differed from those of the first group only in that the albuminuria must have been constantly present in all positions, although increased in grade or amount while the patient was standing. For a diagnosis of chronic latent glomerulonephritis, there must have been a his-

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†From The Mayo Clinic, Rochester, Minn.

TABLE I  
SUMMARY OF MATERIAL

	Cases	Average age at onset, years	Age of oldest patient	Age of youngest patient	Males, per cent	Patients who were recorded to have lordosis, per cent	Elevated blood pressure, patients	Arteriosclerosis, patients	Elevated blood urea, patients	Reduced excretion of phenol-sulphonphthalein, patients	Fixation of specific gravity, patients	Erythrocytes or casts persistent in sediment, patients	Patients traced	Average number of years traced	Nephritis suspected, patients
Orthostatic albuminuria	100	17.24	47	4	62.0	21.0	1	2					64	6.11	1
Albuminuria with an orthostatic response	43	17.79	46	4	74.4	44.5			1			1	43	7.56	2
Latent glomerulonephritis	17	13.35	32	6	70.6	41.1	1					1	17	8.06	
Chronic glomerulonephritis	25		50	10	56.0		8	2	3	2	13	13			25

tory of acute nephritis which apparently had subsided, although albuminuria had persisted. Although it might have been impossible, without the history, to distinguish this condition from uncomplicated orthostatic albuminuria, traces of albumin in the night specimen of urine frequently have occurred. The albuminuria of chronic glomerulonephritis needs no definition.

In the tables when blood pressure is given, it is the average reading, if more than one observation was made, and is expressed in millimeters of mercury. Hemoglobin was estimated in per cent (Dare). Blood urea was expressed in milligrams of urea in each 100 c.c. of blood, as determined by the aeration method. Excretion of phenol-sulphonphthalein was determined according to the modified method of Rowntree and Geraghty. Albumin was

determined by the sulphosalicylic acid method, and was graded from 1 to 4. Specific gravity was obtained by use of the mercury urinometer of Exton.

#### ORTHOSTATIC ALBUMINURIA

We studied 100 cases of orthostatic albuminuria. Of these patients 62 per cent were males. However, it is unfair to compare the incidence by sexes, since we do not know the reasons that originally brought the patients to the clinic. Many came because of the discovery of albuminuria in the course of examination for life insurance, and it is probably safe to assume that more males than females apply for life insurance. The average age when the patients were first seen in the clinic was eighteen and twenty-seven hundredths years, while the average age at the time when albuminuria had been

discovered was seventeen and twenty-four hundredths years. The oldest patient was aged 47 years, and the youngest, four years. Twenty-six per cent of the patients were aged 12 years or less, while 7 per cent were aged 30 years or more. The survey disclosed, also, that orthostatic albuminuria is occasionally seen in late middle life, a fact which needs emphasis. Lordosis was recorded as being present in 21 cases and absent in 11; in the remaining 78 cases nothing concerning it was recorded, but it is probably fair to assume that lordosis was absent in most cases.

Forty-nine patients were either observed repeatedly or were known to have had albuminuria previously, and in these cases the average duration of known albuminuria was six and fifteen hundredths years. Seven of the 49 patients responded to a questionnaire, and indicated that they enjoyed good health and had no symptoms of renal disease over an additional average period of five and eighty-nine hundredths years; results of urinalysis were not reported in their answers. Fifteen patients were observed once only; and they answered the questionnaire, an average of six and one-tenth years later, indicating that they were in good health, but they did not report the results of urinalysis. Thus, 64 patients were traced over an average period of six and eleven hundredths years. The remaining 36 patients were observed once only. One patient with persistent orthostatic albuminuria, one of the 64, was observed over a period of 26 years.

Of the 64 patients traced, 63 (98.4 per cent) were in good health after an average interval of six and eleven hundredths years. One of the 64 pa-

tients (1.6 per cent) had symptoms of renal disease, but urinalysis was not reported in this case. Of the 49 patients who were repeatedly observed, 16 (32.7 per cent) had negative urinalysis after an average interval of six and fifteen hundredths years. Thirty-three of the 49 patients (67.3 per cent) still had albuminuria after an average interval of six and fifteen hundredths years. In 11 cases of the 64, casts or erythrocytes were transiently found in the sediment. In four cases, the value for urea was from 40 to 45 mg. in each 100 c.c. of blood, and in three of these cases excretion of phenolsulphophthalein was normal.

Ophthalmoscopic examination gave evidence of arteriosclerosis in only two cases of the 100. One of these cases was associated with essential hypertension (blood pressure 170 systolic and 130 diastolic), but in this case, six and a half years before, there had been recorded a normal blood pressure and albuminuria of indeterminate type, although tests for orthostatic albuminuria had not been carried out. Albuminuria and occasional casts persisted for three and a half years after the second observation, although there were no symptoms of renal disease. Retinitis was never noted in any case in this group. Only one other patient, and this one was aged ten years, had any evidence of hypertension; blood pressures of 145 and 90 were recorded. This determination was noted as "totally unreliable" however. Ten per cent of the 100 patients had low blood pressure.

#### ALBUMINURIA WITH AN ORTHOSTATIC RESPONSE

In a second group we studied 43 cases, in all of which the diagnosis of

orthostatic albuminuria was entertained. Patients of this group were observed during the same interval as that during which the first group was observed. It is not permissible to make too strict a comparison between this group and the first group, since only those patients who were traced over a period of years are included here.

Males constituted 74.4 per cent of this group. The average age at which the patients were first seen was nineteen and nineteen hundredths years, and the average age at which the albuminuria was discovered was seventeen and seventy-nine hundredths years. These figures are similar to those noted in the first group. The youngest patient was aged four years; the oldest, 46 years. Thirty-nine per cent of these patients were aged 12 years or less, and 14.3 per cent were aged 30 years or more. There was much less notable segregation of cases between the ages of 13 and 29 in this group than in the previous one. Lordosis was present in 44.5 per cent of the cases, absent in 9.3 per cent, and not specified in 46.2 per cent. Thus, among patients of the second series, lordosis was twice as prevalent as among patients with orthostatic albuminuria.

Forty-two of these patients either were observed repeatedly or were known previously to have had albuminuria. The average duration of observation in this group was seven and seven-tenths years. Two patients were in good health an average of six years after observation, but no report of urinalysis was obtained. One patient was observed only once, and responded to the questionnaire four and one-half years later with the information that there was no difficulty but he gave no

report of urinalysis. Thus, 43 patients were traced over an average period of seven and fifty-six hundredths years. Of these patients, 95.4 per cent were in good health, so far as renal or associated diseases are concerned, after an average interval of seven and fifty-six hundredths years; 4.6 per cent (two patients) had symptoms or urinary findings suggestive of renal disease, after the same interval of years, 39.1 per cent of 42 patients had negative urinalysis after an average interval of seven and seven-tenths years.

This group of patients was similar in many ways, to the series of Maclean,<sup>1</sup> of Lee,<sup>2</sup> and of Diehl and McKinlay.<sup>3</sup> However, certain differences may be noted: (1) the patients were all sufficiently concerned about their general health to consult a physician on their own initiative; the patients in the group observed by each of these other writers underwent a required examination; (2) in our series, the albuminuria was usually persistent, in contrast to the observations of Lee and of Diehl and McKinlay; (3) many of Lee's cases were definite examples of orthostatic albuminuria, and cases of orthostatic albuminuria undoubtedly were present in each of the other series; (4) all of the patients in the cases included by the cited writers were males, whereas our series constituted a mixed group; (5) physical exertion as a factor in producing albuminuria did not obtain in the present series, since many of the patients were at rest in bed in the hospital, and (6) it is well to state that no cases of albuminuria following administration of drugs, serums, or albumin were included in our study.

## LATENT GLOMERULONEPHRITIS

Table 2 contains data concerning a group of 17 patients who were known to have had acute nephritis, either in the past or while under observation. The ages ranged from six to 32 years, and only three of the patients were aged more than 21 years. After an interval of eight and six hundredths years, which was the average duration of the time of observation over which results of urinalysis were obtainable, half of the patients were found to have no albumin in the urine, and all were in good health. Lordosis was noted in 41.1 per cent.

Seven of these 17 patients had had scarlet fever, some of whom gave histories suggestive of postscarlatinal nephritis. The remainder gave histories which suggested that they had had acute nephritis, which was either latent when they were first seen at the clinic, as evidenced by the absence of erythrocytes in the urine, or which became latent during the period of observation. Their blood pressures, ophthalmoscopic findings, values for hemoglobin and blood urea and excretion of phenolsulphonphthalein were all within the limits of normal variation.

The principal object in presenting this group is that, aside from the history, 10 of these 17 cases, on a single observation, were in every detail classical examples of orthostatic albuminuria. Such are case 1; case 3, second visit; case 4, second visit; case 5; case 7, second visit; and cases 8, 9; case 10, third visit; 14, and 16. It is of significance that in all of the 17 cases there was an orthostatic response in the albuminuria, and further, that the renal function, so far as it was deter-

mined, was normal in all instances except for the specific gravity determined during the concentration test in two cases. Erythrocytes were observed in the sediment in six cases, in two of which there was acute nephritis at the time. In all but one of these 17 cases there were negative sediments subsequently and there was a question of essential hematuria in this case. Consequently, we feel justified in saying that in this group there was latent nephritis, and in assuming that many of the patients, by the present time, have completely recovered. Furthermore, in these cases which presumably followed acute nephritis there was a period during which, in the process of recovery, an orthostatic response in the albuminuria was a favorable prognostic omen.

Study of the foregoing group shows that often, during the course of latent glomerulonephritis there was an orthostatic element in the albuminuria. Further, during the process of healing, latent glomerulonephritis may exhibit all the characteristics of true orthostatic albuminuria.

## CHRONIC GLOMERULONEPHRITIS

A study was made of 25 patients with chronic glomerulonephritis (table 3). Here we were concerned with the relationship of excretion of albumin to the degree of renal insufficiency as evidenced by tests of renal function. Usually, in cases of glomerulonephritis, the blood pressure becomes elevated sooner or later, during the course of the disease; in cases 2, 3, 9, 10, 11, and 22 (table 3) blood pressures were elevated. Ophthalmoscopic examination disclosed retinal changes in cases 10 and 22. Anemia was present in cases 2, 6, 8, 14, and 18. The value for

TABLE II  
LATENT GLOMERULONEPHRITIS

Case	Years between onset and beginning of study	Etiology	Age, years and sex	Height, inches	Weight, pounds	Lordosis	Blood pressure, mm. of mercury*		Hemoglobin, per cent	Excretion of phenolsulphon-phthalein, per cent	Urine				Sediment	Comment
							Systolic	Diastolic			Routine	Horizontal	Upright	Highest reading†		
1	6	Scarlet fever	12F 21	64 67	108 114	Yes	130 75	78	78	45	1	0	0	1.001	Negative	Orthostatic albuminuria Good health
2	2	Fever?	12F 21	65 68	91 125	Yes	140 80	75	75		2	1	2	1.029	Occasional erythrocytes Negative	Good health
3	5	Nephritis, edema	15M 16 24	65 67 67	120 132 142	Yes	122 80 120 65	78 24	78	50	2	trace	3	1.025 1.001	Occasional cast Negative	Orthostatic albuminuria Orthostatic albuminuria Good health; five years ago negative urine
4	2	Scarlet fever	14M 18 23	67 70 71	131 153 165	Yes	110 75 120 70	80 77 34	80	65	2	trace	2	1.021 1.002	Occasional leukocytes Negative Negative	Orthostatic albuminuria Dental sepsis Good health
5	8	Acute nephritis	22F 30	62 62	116 110		105 60	75 26	75	75	2	0	1	1.022	Occasional casts	Septic tonsils, chronic glomerulonephritis Good health
6	1	Acute nephritis	15M 22	66 70	125 150	Yes	115 70	80 26	80	45	1	trace	2	1.028 1.002	Few leukocytes	Focal nephritis Good health
7	0.5	Acute nephritis	14M 15 18	63 66	89 104		130 75 125 70	72 31 100 82	72		2			1.020 1.001	Erythrocytes graded 1 Negative Negative	Septic tonsils, hypospadias Hypospadias Hypospadias
8	1	Scarlet fever	12M 15	57 67	81 122		95 60 120 80	77 96	77		2	0	2	1.031	Negative	Phimosis, orthostatic albuminuria Orthostatic albuminuria
9	3.5	Scarlet fever	6F 10	46 55	36 54	No	120 80	61 26	61	45	2	0	2	1.036	Negative	Nine months before admission Septic tonsils with head cold Good health
10	2	Influenza	31M 33	70 172	156 200		135 75 125 95	78 80 130 120	78	60	4	1	3	1.032 1.001	Erythrocytes and casts Negative	Focal glomerulonephritis, chronic urethritis, prostatitis Graded 1 Negative

9	3.5	Scarlet fever	6F 46 36 10 55 54	135 75 78 28	60 4 1	3	1.032	1.001	Negative	Nine months before admission with head cold and fever	
10	2	Influenza	31M 70 150	125 85 80 13	85 0	trace	1.030	1.001	Erythrocytes and casts Negative	Focal glomerulonephritis, chronic urethritis, prostatitis, graded 1 Chronic prostatitis, neuromuscular pains, anxiety neurosis, mild residual arteriosclerosis Orthostatic albuminuria, chronic nervous exhaustion; sulfates 2.7 mg. for each 100 c.c. of blood serum	
			36 70 174 No	130 85 100 24	75 1 0	1	1.024		Negative		
11	0.5	Scarlet fever	16M 66 121 Yes 23 69 146	120 70 83 27	50 3 0	trace	1	1.030	Negative	Orthostatic albuminuria Good health	
12	10	Scarlet fever	32M 70 179 37 70 174	130 80 80 26	50 1 0	trace	1	1.031	1.001	Orthostatic albuminuria Good health	
13	1	Tonsillitis?	21M 70 150	140 75 75 17	85 4 2	1	1.021	1.001	Granular casts, erythrocytes, graded 2-3 Erythrocytes, graded 2 Negative	Focal nephritis?  Latent glomerulonephritis Good health	
14	7		15M 70 140 17	100 60 100 20 31†	45 1 1 50 1	0 1 trace	1 1.029 1.032	1.003	Occasional leukocytes	Acute nephritis 3 weeks ago; albuminuria 7 years	
15	0	Acute nephritis	15M	70	1		1.024	1.002	Erythrocytes graded 2, occasional cast	Acute nephritis	
			19 154	125 70 76 24	85 1	trace	1	1.025	1.001	Essential hematuria?	
			22 69 162 No		0			1.014	Occasional erythrocytes		
16	3	Scarlatina	9F 55 62 Yes 16 68 109	73	1 0 0	1	1.009		Negative Negative	Orthostatic albuminuria Good health	
17	0	Subacute nephritis	18M 133 25 71 156	110 65 78 38 110 75 71 32	60 2 80 2		1.020	1.001 1.030	1.002	Erythrocytes, graded 2 Negative	Subacute glomerulonephritis Colloid goiter, albuminuria

\*Ocular fundi were negative in all cases.

†In some cases this represents a reading obtained at routine examination of the urine; in other cases, a reading obtained on concentration test.

‡Non-protein-nitrogen.

TABLE III  
CHRONIC GLOMERULONEPHRITIS

Case	Age, years and sex	Height, inches	Weight, pounds	Blood pressure mm. of mercury*		Blood		Excretion of phenolsulphon-phthalein, per cent	Albumin			Specific gravity		Sediment	Comment	
				Systolic	Diastolic	Hemoglobin, per cent	Urea, mg. for each 100 c.c.		Routine	Horizontal		Upright	Concentration test			Dilution test
1	23F	69	130	125	85	75	30	45	2	2	3	1.020	1.001	Erythrocytes, casts	Chronic glomerulonephritis	
2	21F	64	121	140	100	62	30	75	2	1	3	1.028	1.005	Negative	Chronic glomerulonephritis, insidious	
3	25F	69	158	165	120	72	13	80	1	2	3	1.025	1.003	Erythrocytes, casts	Chronic glomerulonephritis	
4	50M	68	155	120	70	83	25	75	trace	1	2	1.029	1.002	Negative	Chronic glomerulonephritis, latent	
5	16M	61	135	135	85	76	24	30	3	2	3	1.025	1.002	Erythrocytes, casts	Chronic glomerulonephritis	
6	17F	67	146	115	80	68	16	60	2	1	2	1.030	1.002	Negative	Chronic glomerulonephritis, insidious	
7	17M	70	130	130	60	77	24	55	2	2	2	1.021	1.004	Negative	Chronic glomerulonephritis, latent	
8	33F	63	110	120	70	62	20	75	4	4	3	1.020	1.001	Occasional erythrocytes	Chronic glomerulonephritis, insidious, mitral stenosis	
9	16F	66	111	140	90	72	16	75	2	trace	trace	1.030	1.001	Negative	Chronic glomerulonephritis, insidious	
10	46M	65	140	145	95	98	29	75	4	1	1	1.035	1.001	Casts, occasional erythrocytes	Chronic glomerulonephritis, insidious	
11	41M	68	164	145	90	90	36	80	2	trace	trace	1.029	1.001	Negative	Chronic glomerulonephritis, insidious	
12	31M	69	153	145	85	73	30	60	4	3	3	1.030	1.002	Erythrocytes, casts	Chronic glomerulonephritis, insidious	
13	23M	71	157	130	85	91	20	70	2	2	2	1.010	1.009	Negative	Chronic glomerulonephritis, latent	
14	14M	64	101	160	100	61	54	45	4	4	4	1.016	1.004	Erythrocytes	Chronic glomerulonephritis	
15	38M	71	143	130	95	80	22	70	2	1	1	1.026	1.001	Granular casts	Chronic glomerulonephritis	
16	31F	62	117	130	80	75	22	80	2	1	1	1.025	1.001	Negative	Chronic glomerulonephritis	
17	19M	73	154	110	65	80	28	70	2	2	2	1.032	1.001	Negative	Chronic glomerulonephritis, latent	

18	16M	67	145	140	70	75	34	75	2	trace	2	1.030	1.003	Occasional cast, erythrocytes graded 1 to 2	Focal nephritis ?
17				120	80	90	67	2						Negative	
19	67	135	140	90	68	37	40	4	4	3	3	1.016	1.003	Erythrocytes graded 2, casts	Chronic glomerulonephritis ; patient died 3 years later in uremia ; no necropsy
19	31M	69	135	140	95	73	38	65	2	trace	1	1.021	1.001	Erythrocytes, casts	Orthostatic albuminuria, benign hypertension Chronic glomerulonephritis, verified at necropsy
20	39M	73	139	145	90	82	30	60	1	0	trace	1.023	1.002	Hyaline casts, graded 3, erythrocytes graded 2	Chronic prostatitis, focal nephritis ?
21	15F	64	110	110	75	78	30	45	3	0	3	1.013		Negative	Residue of chronic glomerulonephritis
16	64	112	140	90	72	72	35	2	2	2	3	1.016	1.003	Negative	Chronic glomerulonephritis
17	63	108	120	80	70	40	35	1				1.015	1.003	Negative	
17		120	140	90	71	41	15	3	3	3	3	1.014	1.003	Negative	
17		108	135	100	70	80	15	2				1.010	1.001	Negative	
18			130	80	91	10	2				+	1.008			Chronic glomerulonephritis ; verified at necropsy
19															
22	30F	62	156	210	120	77	22	60	4	0	1	1.023	1.001	Casts and erythrocytes	Benign hypertension, chronic nephrosis, orthostatic albuminuria
23	13F	60	74	110	80	100	18		2	1	2	1.026		Occasional erythrocytes	Enuresis
24	22M	69	123	130	85	94	32	80	4	1	3	1.036	1.001	Hyaline casts, erythrocytes graded 1	
24	69	139	110	78					1			1.024	1.001	Negative	Good health
25	10F	54	64	95	75	80			2	0	2	1.030		Leukocytes, graded 1, erythrocytes graded 1	Faulty posture, albuminuria, neuropathy

\*Retinal changes present in cases 10 and 22 only.

blood urea was elevated in cases 14, 18, and 21, whereas elimination of phenol-sulphonphthalein was diminished below the lower limits of normal in cases 5, 18, and 21. In all cases except 20, 21, 22, and 25, albuminuria persisted while the patient was reclining. Impaired concentrating or diluting power of the kidneys was seen in cases 1, 3, 5, 7, 8, 13, 14, 16, 18, 19, 20, 21, 22, and 24. Erythrocytes were noted in the sediment in cases 1, 3, 5, 8, 10, 12, and 14, and in cases 18, 19, 20, 22, 23, 24, and 25 inclusive.

It is important to note that, in all these cases, the glomerulonephritis was sufficiently mild (at least on first observation) to warrant considering the possibility of orthostatic albuminuria. Case 21 fulfilled all the requirements of orthostatic albuminuria on first observation, although fifteen months later renal function had become markedly impaired. This is the only instance of this sequence.

It is apparently possible to make a correlation between the impairment of renal function, as shown by the usual tests of function, and the response of the kidneys to the orthostatic test. Thus, in 19 of the 25 observations (76 per cent) a direct relationship between diminution of excretion of albumin in the horizontal position, as compared with that in the erect position, and the degree of renal impairment as measured by dilution and concentration tests, may be noted. If there was diminution in the amount of albumin excreted, renal function was adequate as measured by the other tests; and, conversely, when albumin did not diminish, renal function was impaired as measured by the other tests. In eight cases there was no diminution in albu-

min in the presence of impaired renal function, and in 11 cases there was diminution of albumin in the presence of good function, a total of 19 cases. In one case there was no diminution of albumin, but good function; and in five cases there was diminution with poor renal function. In grouping these cases allowance was made for the effect on specific gravity of large amounts of albumin.

#### FOCAL INFECTION AND WEIGHT IN ALBUMINURIA

Calvin, Isaacs, and Meyer<sup>4</sup> commented on the high incidence of focal infection among patients with orthostatic albuminuria. In our study, foci of infection occurred with practically the same incidence in association with orthostatic albuminuria, and in association with albuminuria with an orthostatic response. Removal of foci did not appreciably influence the albuminuria in either group. By "foci of infection" we refer to obviously diseased tonsils, teeth, sinuses, or prostate gland, or to a chronic suppurative process, such as bronchiectasis or otitis media. Border-line cases were not included.

Practically all observers have recorded the typical asthenic habitus of patients with orthostatic albuminuria, and the implication is often noted that, with gain in weight after adolescence, albuminuria tends to disappear. In order to gain some accurate information on this point, the recorded weight in each case of orthostatic albuminuria has been compared with the standard normal weight of persons of the same age, sex and height, as given in the tables based on medical actuarial statistics. This has been recorded in percentage of variation above and below

the average normal. Figure 1 shows the averages in the cases of orthostatic albuminuria, and figure 2 the averages in the cases with other forms of albuminuria. It will be seen that there is no striking difference between these groups, both falling chiefly in the normal to minus 10 per cent zone. With

been strengthened by the observations of Russell<sup>6</sup> and of Weiss-Eder.<sup>7</sup> Fishberg<sup>8</sup> inclined somewhat to this view. We are able to add a series of seventeen cases in which true orthostatic albuminuria, or albuminuria with an orthostatic response, dated presumably from acute nephritis. We assume that

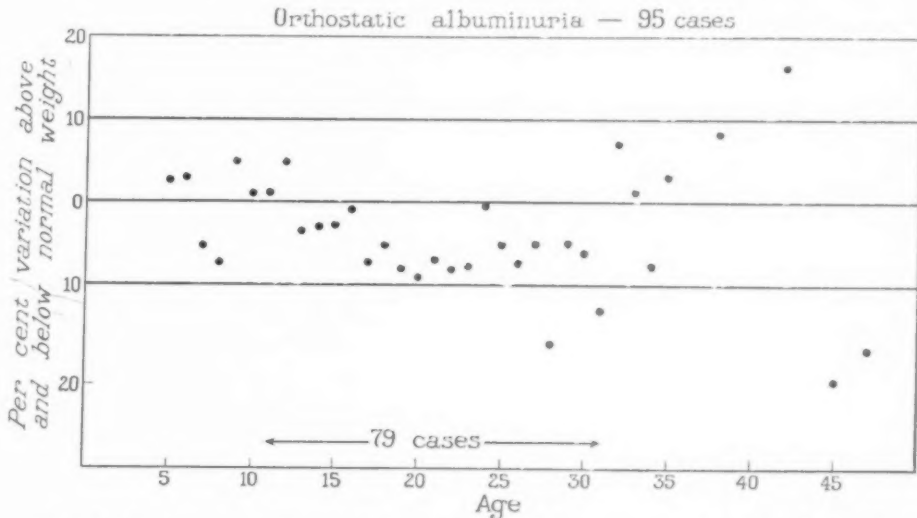


FIG. 1. Average percentage variation, above and below normal, of weight of 95 patients with orthostatic albuminuria. Each spot represents the patients of one age-group. Seventy-nine of the 95 patients were between the ages designated by the positions of the arrow heads, and the weights of most of these 79 patients were within the normal to minus 10 per cent zone.

the passage of years, there is no constant relationship between change in weight and persistence of the albuminuria in cases of orthostatic albuminuria.

#### COMMENT

Among the conflicting reports, the only hypothesis concerning etiology, which has not been refuted, is that of Senator,<sup>5</sup> who reiterated many times in the course of several years, that albuminuria detectable by ordinary clinical tests is never "functional". This hypothesis concerning renal injury has

orthostatic albuminuria or albuminuria with an orthostatic response means persistent renal injury which frequently heals completely. We believe that the burden of proof rests with those who ascribe orthostatic albuminuria to causes other than renal injury. In one case in the first group, the injury presumably went on to nephritis, and cases 20, 21, and 22, in table 3, were definitely cases of chronic glomerulonephritis, although albumin was absent from the night urine.

It is possible to avoid error, to a great extent, by insisting on the fol-

lowing points before making the diagnosis of orthostatic albuminuria: (1) absence of even traces of albumin in the urine excreted with the patient recumbent; (2) absence of persistent erythrocytes or casts, or more than an occasional erythrocyte or cast in the sediment; (3) absence of a history or of physical signs of nephritis or ne-

more so than the other patients studied, and changes in weight have no effect on the incidence of albuminuria. It should be noted that the albuminuria may persist through middle life.

Among patients who have albuminuria with an orthostatic response, the prognosis is almost as good, but the diagnosis must be established with the

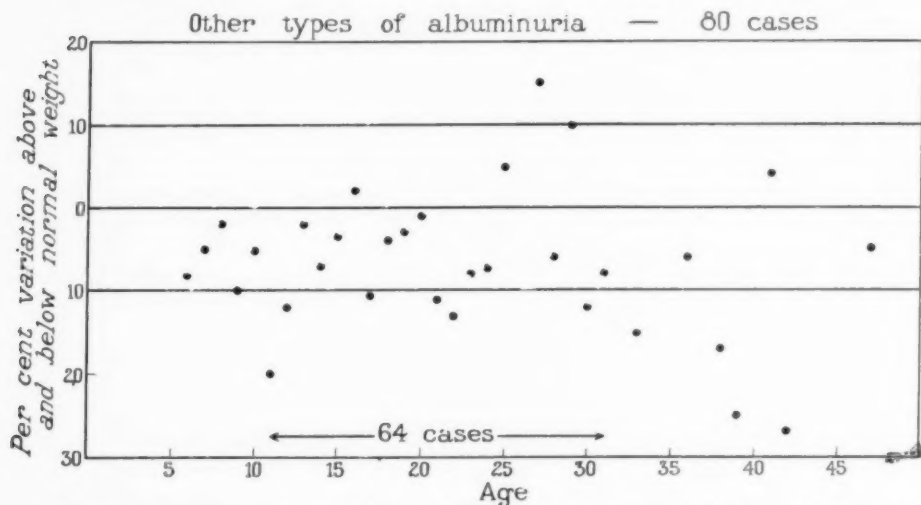


FIG. 2. Average percentage variation, above and below normal, of weight of 80 patients with albuminuria of other than orthostatic type. Each spot represents the patients of one age-group. Sixty-four of the 80 patients were between the ages designated by the positions of the arrow heads, and the weights of most of these 64 patients were within the normal to minus 10 per cent zone.

phrosis or associated vascular changes; (4) normal renal function, as measured by the usual tests, and (5) observation of the patient over a period of several months. A correct diagnosis of orthostatic albuminuria carries with it a prognosis of good health and longevity in 99 per cent of cases, and a probability that, in 33 per cent, the urine will become free of albumin. There is no evidence that foci of infection play any part in the causation of orthostatic albuminuria. The patients are slightly underweight, but no

same care as in orthostatic albuminuria. We believe that albuminuria with an orthostatic response indicates a more marked degree of renal injury.

When a diagnosis of latent glomerulonephritis is considered, a period of several months of observation is necessary, to be sure that one is not dealing with slowly progressive chronic glomerulonephritis. Although the outcome in our small group of cases of latent glomerulonephritis was as good, or was better, than that in the groups of cases of orthostatic albuminuria, or of cases

of albuminuria with an orthostatic response, we feel that, in general, the prognosis should be more guarded. The presence of an orthostatic element in all of our cases may well have a relationship to their unusually good outcome. The development of orthostatic albuminuria in the course of acute nephritis seems to indicate partial recovery, and may be of aid in establishing a prognosis.

Although the existence of an orthostatic element in chronic glomerulonephritis has been frequently observed, we are not able to find record of any attempt to correlate it with tests of renal function.

The etiology of orthostatic albuminuria is not known. However, a few facts about man's excretion of urine due to his upright position, may help to explain orthostatic albuminuria. For instance, excretion of water by normal kidneys has been shown to be decreased by the upright position.<sup>9</sup> There is some evidence in favor of the belief that excretion of such a substance as urea may, also, be so affected. If some sort of mild renal injury is assumed, then the following concepts are applicable: when the patient is recumbent, function is enhanced, water and such substances as urea are excreted more easily, and albumin not at all. As soon as the upright position is assumed, the kidney is not able to readjust itself, and there is loss of albumin. Furthermore, in support of this view, we have shown that in chronic glomerulonephritis, when

renal injury progresses sufficiently to be demonstrable by the usual tests of function, the element of orthostatic albuminuria disappears. Also, in selected cases, during recovery from acute nephritis, a period characterized by orthostatic albuminuria is not uncommon. Therefore, orthostatic albuminuria is probably in the range of mild renal pathologic physiology.

#### CONCLUSIONS

1. Strict diagnostic criteria must be observed before a patient is considered to have orthostatic albuminuria.

2. The prognosis is excellent in cases of orthostatic albuminuria, although the albuminuria may persist through middle life.

3. The diagnosis of albuminuria with an orthostatic response requires similar careful consideration, and carries almost as good a prognosis.

4. Among patients who have had acute nephritis, the development of an orthostatic element in the albuminuria apparently indicates partial recovery and a good prognosis.

5. In chronic glomerulonephritis there is some evidence that the presence of an orthostatic element in the albuminuria indicates adequate renal reserve, and its disappearance may be a sign of renal insufficiency.

6. From the data presented regarding the etiology of orthostatic albuminuria it would appear that the burden of proof rests with those who do not consider it due to renal injury.

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# Addison's Disease and Its Relation to Experimental Adrenal Insufficiency\*†

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ALTHOUGH the first accurate description of the adrenal glands is usually accredited to Eustachius, in 1563, very little further progress was made in the study of their structure or physiological significance for nearly three centuries and practically all of the further additions to our knowledge have been made within the past eighty years. Modern interest in the adrenals dates from Addison, who published in 1855 the clinical observations on the disease which bears his name.

In all mammals, including man, the adrenal glands are paired organs, each composed of two distinct parts. The outer layer, or cortex, forms roughly two-thirds to three-quarters of the whole, and this surrounds the inner portion, or medulla, which is of distinct and separate embryological origin. Until very recently the attention of most investigators has centered upon the medulla, which has been shown to be closely related in its origin to that of the nerve cells of the sympathetic ganglia and in its later

development and functional significance to the sympathetic nervous system.

There is both an anatomical and a physiological reason for the greater interest which has been displayed in the adrenal medulla. In 1865 Henle first showed the peculiar affinity of the medullary tissue for the salts of chromic acid, and the characteristic brownish-yellow staining reaction of these chromaffin, or chromaphil cells when treated with this chemical was of prime importance in their identification.

The second reason for the greater interest in the adrenal medulla lies in the fact that extracts of this chromaffin material possess peculiar and characteristic physiological properties, readily observed and measurable with relative ease, although with uncertain accuracy. The substance itself which we now know as adrenalin was finally obtained in crystalline form and subsequently produced synthetically just about thirty years ago. For a number of years the discovery of adrenalin naturally focused attention upon the adrenal medulla to the exclusion of interest in the cortex, since it was demonstrated with reasonable conclusiveness that adrenalin originates solely in the medulla, its presence in the cortex being due to postmortem diffusion. The advances which followed the isolation

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of adrenalin furnish a striking example of the fact that progress in knowledge of any endocrine gland secretion is in direct proportion to the availability of a simple quantitative measure of its physiological effects.

Chromaffin tissue is widespread in its distribution. Stilling, and later Kohn, showed that groups of cells occur throughout the course of the sympathetic nervous system, either as microscopic clusters in the ganglia or as macroscopic bodies in the sympathetic plexuses called "paraganglia". In addition to similarity in morphology and in the chromaffin reaction, extracts obtained from this extra-medullary tissue exhibit similar physiological properties to like preparations derived from the medulla itself. Indeed, according to Biedl, in the new-born, in whom very little adrenal medulla exists, the action of these extra-adrenal extracts, particularly those from the abdominal chromaffin body, are more effective upon constriction of blood vessels than those from the adrenal medulla itself. This abdominal chromaffin body remains of considerable size until the child is one year of age, after which it degenerates. In other forms, as in the dog, cat, and rabbit, it is an organ of significant size throughout life. Kohn showed by accurate determinations of the respective weights that the abdominal chromaffin body in the adult dog may represent as much as one-quarter of the total weight of the medulla itself.

Studies leading to such knowledge as we now possess of the physiological significance of the cortex really antedate those on the medulla, although they were not at the time so recognized. The original description of Addison's disease was the stimulus which

led Brown-Sequard in 1857 to test the effect of removal of the adrenals in a number of different species, including rabbits, dogs, guinea-pigs and cats. A fatal result invariably followed their bilateral removal within thirty-seven hours and this led him to the view that the adrenals are essential to life. There is no doubt that this correct conclusion, in the light of present day knowledge, was based upon experiments in which the animals died, not of adrenal insufficiency, but of surgical shock or of sepsis. It is possible with proper surgical technic, using dogs, even when both glands are removed at one operation, to have survival without any treatment for at least seven days. The effect, however, is ultimately that described by Brown-Sequard. If insufficient accessory adrenal tissue is present, the animal invariably dies.

The question then arose as to whether the part of the gland indispensable for life was the medulla, the cortex or the adrenal tissue as a whole. Through the efforts of a considerable group of observers it has been shown during the past two decades that the cortex of the gland is the vital structure, since destruction of the medulla by extirpation or by a number of other means, such as cauterization or radiation, permits the animal to live on. So long as the cortex, or at least a fraction of it (from one-fourth to one-eighth), is left intact, the animal does not seem to suffer ill effects. It has, therefore, been generally accepted in recent years that the cortex is the essential structure. The medulla and the chromaffin tissues generally have been tacitly relegated to a position of minor importance. This view has undoubtedly been strengthened by the success which has attended

substitution therapy with lipid soluble extracts of the cortex in totally adrenalectomized animals, as demonstrated by Hartman, by Swingle and Pfiffner, and by others within the past two or three years.

It is well to bear in mind, however, that the question of the importance to life of the chromaffin tissues as a whole has never been brought to rigorous test. Owing to their widespread distribution they cannot be completely extirpated, as can the cortex in most forms, where accessory cortical tissue in significant amounts does not exist. We must conclude that the indispensability of the medulla yet remains to be disproven, and that it is at the present moment unknown whether the close juxtaposition of these two portions of the adrenal gland differing so widely in origin, morphology, and chemical properties, is pure accident or is of vital and fundamental significance.

Certain facts, however, have been gathered which make it appear that the close approximation of these two tissues in the mammal may not be altogether a coincidence. In some of the lower vertebrates, as in the elasmobranch fishes, the tissues which correspond to the adrenal cortex and medulla are separated, the cortex being represented by the interrenal body and the medulla by the paired bodies which lie close to the ganglia of the sympathetic chain. In birds and reptiles, and in amphibians, the renal and adrenal tissues interlock. It is only in mammals that the same condition is found as in man—the adrenal is composed of a central medulla with an enclosing cortex.

In most mammals, as is well known, the cortex is divided by the morpholo-

gists into three zones. The cells in the central portion are arranged mainly in columns, the zona fasciculata. The portion next to the medulla is a network of trabeculae, the reticularis. At the surface the columns end in rounded terminations, the so-called glomerulosa.

The blood supply of the adrenal gland is of particular interest. Per unit of weight it is more abundant than that of any other body organ, being estimated as 6 to 7 c.c. per minute for each gram of tissue, higher even than the thyroid, which comes next with 5 c.c. per gram per minute. The arteries divide in the cortex into capillary plexuses which fuse into sinuses in the reticularis, the innermost zone of the cortex, and go over by numerous and free communication into the venous sinuses of the medulla. A second supply to the medulla is from branches which perforate the cortex without division. Present evidence indicates that a very considerable proportion of the adrenal blood supply passes first through the cortical layers of the gland and thence into the medulla, so that materials given off into the blood stream in the cortex, in large part, at least, have opportunity to come into contact with the cells of the medullary portion of the gland. The blood from both regions unites to pass out in the same venous channels.

Because of the fact that it has been shown to be an indispensable portion of the gland, attempts to isolate an extract which would prolong the lives of adrenalectomized animals have usually been made with material from the dissected adrenal cortex alone. The medulla, containing the bulk of the adrenalin, was discarded. Improved technical methods, however, have recently

made it possible to get rid of adrenalin and other toxic products with comparative ease, so that the whole glands may be used for the manufacture of the extract, thus avoiding the laborious preliminary separation of medulla and cortex.

Pfiffner and his collaborators at Princeton, using the method of biological assay of the cortical hormone, which was devised last year in our laboratory at Baltimore and which is based upon the minimal per kilo maintenance dose in the adrenalectomized dog, have recently shown that extracts prepared according to the Pfiffner-Swingle method from whole beef adrenal glands have several times the potency of extracts made from dissected beef cortex alone, based on equivalent weights of tissues. This remarkable fact we are able to confirm. Extracts of dissected cortex material alone have an assay value of six to ten dog units per c.c. of material, while extracts prepared from whole beef adrenal glands may have an assay value of forty units per c.c. or even more. The method of assay which we have employed is, we believe, accurate to within 25 per cent of the true value. If well-nourished animals in prime condition are used the results under these conditions are readily reproducible.

This increase in the potency of extract prepared from the whole glands as compared with that from the dissected cortex is somewhat difficult to interpret on the basis of the long held assumption that the cortex as a whole is the site of origin of the hormone essential to life. This difficulty is increased by a recent paper by Cleghorn,<sup>1</sup> who found that extracts of the (skate)

elasmobranch interrenal body, which as we have stated above is distinct in this form from the segmentally arranged chromaffin bodies, and may be dissected quite separately from them, is without effect in reviving or maintaining the adrenalectomized cat.

In an attempt to throw further light on these puzzling and conflicting findings, my associates, Dr. J. H. Trescher, and Dr. L. J. Soffer, and I have undertaken comparative assays of extract made from: (1) cortical tissue prepared free of medulla by taking thin slices from the periphery of the gland cleaned and dissected away from the surrounding tissues and fat; (2) cortical tissue prepared in the usual manner by splitting the gland longitudinally and dissecting out the medulla; (3) the medulla tissue dissected quite free of cortex; and finally (4) the whole gland material. The material for this study was obtained on the slaughtering floor of one of our large abattoirs immediately after removal from the beef carcass. As rapidly as it was dissected out it was thrust into 95 per cent alcohol to prevent destructive enzyme activity, and frozen solid with carbon dioxide snow. The following assay values on glands so prepared and derived from the same source have been obtained for equivalent weights of tissue:

#### PREPARATION OF EXTRACT

1. Cortical tissue from the periphery, not in contact with medulla, less than 3 dog units per c.c.
2. Cortical tissue prepared in the usual manner, 8 dog units per c.c.
3. Medullary tissue, 8-10 dog units per c.c.
4. Whole gland tissue, 15-20 dog units per c.c.

These results indicate the higher

concentration of the potent principle as we approach the medulla and the relatively low concentration in the outer part of the cortex of the beef adrenal. Complete separation of cortex and medulla is very difficult. Portions of medullary tissue must be present in the dissected cortex prepared according to the original technic, while the dissected medullary tissue undoubtedly contains fragments of cortex, especially of the reticular layer.

In the light of our fragmentary knowledge both of the chemical properties and of the function of the new hormone, it is most plausible to account for its greater concentration near or in the medulla on the supposition either that it is stored in the larger venous sinuses, or that it is bound to some protein or other structure present in the medulla, so that diffusion from cortex into medulla may continue and increase its concentration in the latter portion of the gland.

It may be interesting, however, to draw your attention to another possibility to account for this curious and unexpected distribution of the hormone within the gland. This is that the site of final activation of the so-called cortical hormone (or "cortin") actually lies in the outer portion of the medulla itself, or in the reticular layer of the cortex which immediately adjoins it. The findings are compatible with the assumption that the cortex elaborates a precursor which is converted into the active substance in this region of the gland. The blood supply of the adrenal gland, in which blood from medulla and cortex are joined together in this border area would favor such a possibility.

The mechanism above outlined would explain not only the indispensability to life of the interrenal body of the elasmobranch, as shown by Biedl, but, on the other hand, the seemingly contradictory finding that extracts of this organ, according to Cleghorn, do not contain the "life" hormone. It will also explain the variations in amount of active material in the several parts of the gland as found above. The survival of animals in which the medulla of the gland has been destroyed or removed, leaving the cortex intact (assuming that such complete elimination is really possible) may be explained by the presence of accessory medullary tissue which, as I have just stated, occurs in large amounts. The presence of smaller amounts of the hormone in the outer layers of the dissected cortex could then be explained in the same manner as the occurrence of adrenalin in the cortex, namely, as due to diffusion into the outer cortical portion of the gland post mortem. The enhanced potency of material derived from the whole adrenal glands prepared in the usual way may well be due to the intimate admixture of the chopped-up tissue during the course of preparation of the extract, or to lessened exposure to the air.

The main cause of Addison's disease is bilateral tuberculosis of the adrenal glands. It was formerly believed that the adrenal infection is primary, but it is now realized that this lesion is usually associated with latent or active tuberculosis elsewhere in the body, probably in most instances in the lungs. Tuberculosis of the adrenals is a relatively rare disease having, it is said, about the same incidence as tubercu-

losis of the skin. The tuberculous lesion appears to attack the medulla first and later the cortex. The latter always seems to be affected, however, in reliable reports of Addison's disease. Wiesel found in a fifteen-year-old tuberculous patient with complete destruction of the medulla, but intact cortex, no symptoms of the disease, although the paraganglia, significantly enough, were much enlarged.

In approximately one-fifth of the published cases but in a larger proportion of our present series, the lesion found at autopsy in the adrenal glands is that of primary cortical atrophy. A very considerable number of such cases has now been reported, and it is of interest to note that in them, in contrast to the cases of tuberculosis of the adrenals, it is the cortex which is first and principally affected while the medulla is seriously altered only at a later period. Our fatal cases of Addison's disease associated with this primary cortical atrophy have been studied by Duff and Bernstein<sup>2</sup>; we have had four come to autopsy. The destructive process was a progressive necrosis of cortical cells with collapse of the stroma. The reticular zone disappeared first and of the two other zones the outer one, the glomerulosa, persisted longer. Regeneration appeared as islands of newly formed cells at the periphery. More or less dense infiltrations of lymphocytes were always present in the medulla and among the remains of cortical tissue. The necrosis of the cortical cells was accompanied by relatively little fibrosis, the outer capsule simply collapsing down to the medullary tissue.

Duff was able to find four less ad-

vanced cases of adrenal atrophy in which a similar destruction had taken place, with small lymphocytic accumulation and without changes in the medulla. In these cases without symptoms of Addison's disease, the primary lesion was in the cortex, and the reticular zone was most susceptible, the glomerular most resistant, to destruction.

It seems to us of importance from the point of view of therapy that areas of regeneration occur in the injured glands. The quick response of the remaining cortical tissue to the stimulus of deficiency is striking. In the experimental animal, after removal of one gland, hypertrophy of the remaining adrenal gland is very rapid, and quite definite in the dog within three or four weeks. This hypertrophy is decidedly greater in the presence of infection, distemper in the dog being an especially effective stimulus. It is not unusual in such cases to find the second gland double the weight of the one first removed. This increase is confined so far as we can determine to the cortical portion. When sufficient extract is supplied to the adult male dog from which one gland is removed this hypertrophy is not found, indicating that lack of this material is the adequate stimulus for production of the hypertrophic change. Injections of the extract will not, however, prevent hypertrophy of the remaining gland in a growing animal, or in the presence of malnutrition, or of an intercurrent infection, even in doses per kilo of body weight which are otherwise effective in the healthy adult. We believe this to be suggestive evidence that products of the cortical tissue are required in greater amounts by the growing animal,

as well as by the animal during the course of an infection, and that further studies along this line may be of help in reaching a better understanding of this phase of cortical function.

One of the cardinal features of Addison's disease is pigmentation. In many it is the first symptom observed and often one finds that the earliest change the patient notes is that of a summer's tan which does not fade. It may be present for many years and it has been repeatedly observed that such cases are apt to be more prolonged and to run a more benign course than those ushered in by asthenia and muscular weakness. A recent case observed by us is of interest:

G. F., a white man of 55, works for a life insurance company which gives periodic health examinations to its employees. Owing to this it is known that he has had low blood pressure since 1917. During 1917 and 1918 he was in a sanitarium for sixteen months with pulmonary tuberculosis. One daughter has died of pulmonary tuberculosis, but the contact with the patient was not close. He has felt quite well. There have been no gastrointestinal symptoms and no muscular weakness prior to his present illness. He came to the hospital this autumn with influenza complicated by pneumonia and there it was noted that he had marked and characteristic pigmentation of lips and buccal mucosa, which he stated on questioning had been present for many months. During recovery from his influenzal infection the asthenia has improved and at the present time he is free of symptoms. He has never received cortical extract.

We have here a patient whose history and appearance is highly suggestive of Addison's disease, with proven hypotension for many years and with pigmentary changes for many months. It seems quite possible that in this instance we are dealing with tuberculosis of the adrenals and that the process

has so far attacked chiefly the medulla while the cortical portion is as yet largely unimpaired.

Speculation as to the relationship of the pigmentation to the disease has naturally centered about the close similarity of chemical structure between adrenalin and the skin pigment, melanin. It has been suggested that failure of the gland to utilize the natural adrenalin precursors to form adrenalin has led to their vicarious utilization in the skin in the formation of increased amounts of melanin. The supposed precursor most popular in the minds of investigators is dioxyphenylalanin or "dopa", which has been studied by Bloch and his pupils. Unfortunately, it has not been possible to produce such skin pigmentation experimentally by removal of the adrenal glands in animals and the positive results reported from time to time cannot be regularly reproduced. Scars, pressure, exposure to various chemical and physical agents, including light, produce no pigmentation not also to be observed in control animals. The injection of dioxyphenylalanin itself in rats and in dogs without adrenal glands is without effect. Patients with Addison's disease during the relapse often show marked increase in pigmentation, and improvement is frequently but not regularly associated with its partial disappearance. With the aid of Professor Max Brödel and his pupils we have been measuring the depth of pigmentation in our patients over definite skin areas during the various phases of the disease. We find that when these changes are measured by such objective criteria our clinical impressions have often proved very faulty. Increases appear rather quickly especially during re-

lapses but disappear very slowly, probably by wearing away of the basal cell layer in which the pigment is deposited in the natural course of skin growth. Differences measured over the course of months are indeed quite definite, but no marked disappearance of the pigmentation has occurred even after much extract has been given.

Now as to the results of treatment of patients with the new cortical extract. We have treated during the past two and one-half years thirteen patients whom we regard as definitely suffering from Addison's disease. Of these, seven have died. The diagnosis in all of them was confirmed by autopsy. (Table 1) C. L., the first case

assay, probably due to imperfect preservation of the glands at the abattoir during the hot weather. F. R. died at a sanatorium of disseminated tuberculosis throughout the body. His condition was hopeless from the outset and the wisdom of treating such cases, when limited supplies of the extract are available, is of course open to grave doubt. The other four fatal cases were those due to cortical atrophy and the lesions found have already been discussed.

It is quite evident that the hopes aroused three years ago as to the value of the cortical extract or cortin in the treatment of Addison's disease have not met with as complete satisfaction

TABLE I  
CASES OF ADDISON'S DISEASE TREATED WITH ADRENAL CORTICAL HORMONE  
WITH FATAL OUTCOME

Patient	Age	Sex	Duration of illness before treatment	Duration of treatment	Number of relapses	Weight gain after treatment	Outcome Autopsy Diagnosis
C.L.	50	F	6½ yrs.	8 wks.	4	No increase	Tuberculosis of adrenals
E.S.B.	34	M	22 mos.	8 mos.	3	No increase	Cortical atrophy with symptoms of asthma
R.M.C.	36	F	8 yrs.	9 mos.	6	No increase	Cortical atrophy; cirrhosis of liver with jaundice
M.S.	37	F	4½ yrs.	15 mos.	4	No increase	Cortical atrophy; acute fibrinous pericarditis
M.D.	35	F	6 mos.	10 mos.	2	No increase	Cortical atrophy.
G.K.	48	F	4 yrs.	23 days	1	No increase	Tuberculosis of adrenals and cold abscess of rib
F.R.	42	M	11 mos.	80 days	3	No increase	Tuberculosis of adrenals, lungs, kidneys and liver

treated in the fall of 1930, did not receive adequate amounts of extract according to our present standards. G. K. was treated for twenty-three days last summer with an extract of low potency, as was later found on

as was originally anticipated. There can be no doubt, we believe, of the value of the material in the acute relapse of the disease. It should be given in large amounts at as early a time as possible. We have never seen evidence

of overdosage in the experimental animal. We have administered 100 c.c. intravenously to an 8 kg. dog without the slightest evidence of toxicity and we have never noticed any harmful effect clinically from the use of any of the extracts prepared in our own laboratory. It appears possible that the extract alone in certain cases without the aid of any accessory agent can relieve the acute crisis, as is indicated by

circulatory collapse. Insofar as the cortical hormone appears to restore the blood volume and blood pressure to a normal level, the regulation of these functions either directly or indirectly must be regarded as one of its essential rôles.

On the other hand (table 2), the value of continued treatment with cortical extract during the intervals of comparative well being and adequate

TABLE II  
CASES OF ADDISON'S DISEASE TREATED WITH ADRENAL CORTICAL HORMONE  
SHOWING IMPROVEMENT

Patient	Age	Sex	Duration of illness before treatment	Duration of treatment	Number of relapses	Blood pressure change	Gain in weight	Present condition	Clinical Diagnosis
D.D.	18	F	5 yrs.	16 mos.	5	none	none	Fair	Tuberculosis
A.O.	61	F	3 yrs.	16 mos.	1	94/68 to 116/82	9.4 kg.	Good	Atrophy (?)
C.G.	29	F	5 mos.	19 mos.	none	none	none	Good	Tuberculosis
C.K.	21	M	14 mos.	12 mos.	1	none	4.4 kg.	Good	Tuberculosis
P.G.	39	M	10 mos.	10 mos.	none	none	2.2 kg.	Fair	Atrophy (?)
R.L.	48	F	9 mos.	4 mos.	1	none	6.5 kg.	Good	Tuberculosis (?)

the recent report of Albright and Baird.<sup>3</sup> Our experience leads us to agree with Loeb<sup>4</sup> in his conception of the Addisonian crisis as a condition of shock, and we believe the value of the usual measures to combat shock and particularly the importance of intravenous saline and glucose solutions is definitely proved. The crisis of Addison's disease is strictly analogous to the condition of insufficiency in the adrenalectomized dog following withdrawal of extract and responds to the same treatment. In all essential particulars they are identical with the condition of shock as seen in both surgical and medical practice. Untreated, death occurs as a result of tissue dehydration, hemoconcentration, and

circulation must be regarded with greater reserve. We have now under observation two patients treated for approximately twenty months. The condition of one of the two is essentially stationary while the other shows slight improvement. Gain in weight has not been striking; no marked change has occurred in the blood pressure, and the pigmentation, while less in amount, is not decidedly improved in either of these patients. Two other cases, both under extract treatment now for about one year, are in very good condition. A comparison of the cases with fatal outcome with those in which more or less improvement has taken place indicates that in the latter group fewer relapses have occurred.

It seems altogether likely that in the prevention or amelioration of repeated relapses by the early use of the cortical extract when symptoms first appear, a definite step may be taken towards the prolongation of life. The average duration of the disease in our group at present under treatment is a little over two years. In a large proportion of cases the disease has an essentially chronic character, although the average duration of life in patients untreated in the large Mayo Clinic group is said to be 16.5 months. Actual prolongation of life therefore has not yet been conclusively demonstrated. It is quite evident that a much greater experience is needed for the proper evaluation of this therapeutic agent upon the eventual course of the disease and its ultimate prognosis.

In determinations of the minimal amounts of extract required for maintenance of the adrenalectomized dog, we have found that the use of certain oils by mouth often permits of lower extract dosage than would otherwise be required. Of the oils so far examined, cotton-seed oil has proved most effective. The action of cotton-seed oil in enhancing the effect of the cortical extract upon the adrenalectomized dog has led us to apply this material to the treatment of our patients with Addison's disease during the intervals of comparatively good condition. We believe that the clinical improvement and absence of relapses under such treatment is sufficiently suggestive to merit further study of its efficacy. The employment of these oils is of little or no value during the relapse, when the extreme nausea and vomiting make their use by mouth very difficult if not impossible. The reasons for the effec-

tiveness of these oils is at present under study. One point only may be observed. The maintenance of good nutrition in the experimental animal is of great importance in lowering the extract requirements. We administer clinically as large doses of the oil as may be tolerated without great distaste, nausea or other undesirable symptoms.

Most important of all as an adjunct to the treatment of the acute relapse with the cortical extract, is the use of large amounts of sodium chloride. If tolerated it should be given by mouth, but it must be administered intravenously and subcutaneously if necessary. Stress must be laid on early treatment. Most patients tolerate well two or three one-gram capsules of sodium chloride when given immediately after the ingestion of food or fluids. Great care must be exercised to avoid increasing the nausea which is inevitably associated with this condition. It is quite definitely shown that patients in relapse usually have marked dehydration and that this underlies the condition of shock. Our unpublished data collected over the past three years, as well as the recently published paper by Loeb<sup>4</sup> indicates that the acute relapse is characterized by marked loss of sodium and chloride from the blood plasma, and, especially in the earlier stages, increased excretion of these substances in the urine. Even where the plasma chloride content has dropped to 75 mil. eq. per liter (435 mgs. as NaCl per 100 c.c.), sodium and chloride are still excreted in the urine. Further, we have been able to produce an acute relapse in two patients merely by placing them on a salt free diet for four

days. Patients should be cautioned to use ample salt in their diet, and indeed one of our patients (M. S.) particularly craved salt pork, stating that she felt much better when she ate this food.

In conclusion we may summarize our findings as follows: A comparison of the phenomena observed clinically during the relapse of Addison's dis-

conditions in both medical and surgical practice.\* It would appear that these are symptoms due primarily or secondarily to a deficient supply of a substance elaborated in the adrenal cortex. (Table 3).

When we come to the maintenance of patients as well as experimental animals not in a condition of shock, however, the points of resemblance are

TABLE III  
COMPARISON OF THE PHENOMENA PRESENT IN MEDICAL OR SURGICAL SHOCK, IN THE RELAPSE OF ADDISON'S DISEASE, AND IN ADRENAL INSUFFICIENCY PRODUCED BY WITHDRAWAL OF CORTICAL EXTRACT IN THE ADRENALECTOMIZED ANIMAL

	Medical or Surgical Shock	Relapse in Addison's Disease	Adrenal Insufficiency in the Adrenalectomized Dog
Body temperature	Low	Low	Low
Hypotension	Frequently present	Present	Present
Blood non-protein-nitrogen, urea, red cell count, hemoglobin and hematocrit.	Frequent	Common	Present
Pulse	Increased	Increased	Increased
Blood non-protein nitrogen, urea, plasma proteins	Frequently increased	Usually increased	Increased
Nausea, vomiting	Common	Common	Common
Plasma chlorides, bicarbonate, total base and sodium		Low	Low

ease with those of adrenal insufficiency in adrenalectomized dogs after withdrawal of extract, reveals important similarities. The points of resemblance are the extreme muscular weakness, the anorexia, vomiting and diarrhea, the lowered general bodily activity associated with lowered body temperature, blood pressure and general metabolism, the increased concentration of the blood, and finally, the changes in certain chemical constituents of the blood some of which are fairly characteristic of the condition of shock as met with in a variety of pathological

not so striking. Adequate dosage of cortical extract in the dog appears to maintain normal nutrition and weight and to preserve life indefinitely. The blood pressure is normal, there is no hypoglycemia, no increased pigmentation and no change in the basal respiratory metabolism. It has seemed that over a long period of time a moderate grade of secondary anemia develops.

\*These changes consist in lowered plasma total base, sodium, bicarbonate, and chloride concentrations. The concentrations of plasma potassium, magnesium, proteins and inorganic phosphate are increased.

In contrast, the patient with advanced Addison's disease, not in relapse, even when given large amounts of a potent preparation of cortical extract continues to exhibit hypotension, usually hypoglycemia, and no striking amelioration in the pigmentation which is characteristic of the disease and without which we are unable to make a diagnosis. The effect on weight and nutrition is variable and sometimes very slight. The basal metabolic rate is lowered in most patients. Well marked anemia is uncommon.

It is a striking fact that the pathological phenomena singularly unaffected by administration of the cortical

hormone in Addison's disease in man, namely, hypotension, hypoglycemia and pigmentation, are just those which do not occur during treated suprarenal deficit in the dog. They are phenomena which a considerable body of experimental evidence associates with disturbance of medullary function and particularly with that of adrenalin. We believe that the evidence is increasing that Addison's disease is probably dependent on disturbed function of both cortex and medulla, and that these two portions of the adrenal gland have reciprocal relations of such a nature that damage to the one produces disturbance of function in the other.

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# The Influence of Age in the Experimental Production of Hypertrophic Arthritis\*

## Preliminary Report

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IN a previous communication, evidence has been adduced by the present writers which indicates that it is possible to induce an overgrowth in the patella of dogs, characteristic of hypertrophic arthritis, by ligation of the blood supply to that structure. The changes resulting consisted in a marked increase in size of the patella which reached its maximum about nine months after operation. Control experiments showed that this result was not due to the trauma of operative procedure. The phenomena accompanying overgrowth were essentially those characterizing hypertrophic arthritis as seen in human beings, but there were also some evidences of atrophic arthritis, such as slight erosion or rarefaction of the margins of the patella together with general thickening and adhesions of the soft structures of the joint as a whole, making dissection difficult.<sup>1</sup>

Following increasing recognition of the two main types of arthritis first emphasized in this country by Nichols and Richardson<sup>2</sup> in their classic monograph, studies have been conducted by many workers, having for their aim

determination of the etiology of the two types of the disease. These studies have usually indicated, with some exceptions, that arthritis constitutes a syndrome having diversified pathologic manifestations and many etiologic factors. This point of view is that which Nichols and Richardson endeavored to establish, although a few subsequent workers have held a rather more dogmatic attitude which regards the two types of the disease as wholly distinct and referable to quite different etiologic causes. Supporting evidence for the former view is found in the accepted etiologic importance in both types of the disease of such factors as heredity, bodily configuration, imbalance of the nervous system, and dysfunction of the gastrointestinal tract, as well as in the common response of these types to certain forms of therapy. Focal infection, which has long and properly been emphasized, is now regarded as constituting often a precipitating or additional factor only, and one which, although contributory to poor health, may, even when demonstrably present, have little or nothing to do with the actual arthritic process. The most significant advances recently made in

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treatment center around this broader appreciation of the subject.

Notwithstanding this widened outlook, there is avowedly much to be determined as to the extent to which the two types of arthritis, atrophic and hypertrophic, overlap; the extent to which they constitute separate processes; and the extent to which they require different forms of therapy. It is accepted that the clinical phenomena of the two types, as well as the osseous picture by X-ray or "en gros", offer sharp contrasts, but some of the considerations enumerated above strongly suggest some commonality of etiology and of certain physiological deviations underlying the disease as a whole. One of the outstanding observations relating to arthritis as seen in the human being is the fact that atrophic arthritis is, by and large, a disease of the first half of life, and hypertrophic arthritis, by and large, is a disease of the latter half of life. There are exceptions to this, in that atrophic arthritis may appear as late as the eighth decade and hypertrophic arthritis may appear early in mid-life, or, according to some recent observations of Matz,<sup>3</sup> even earlier. In general, however, any observations of a large series of arthritics will show that atrophic arthritis tends to disappear at an age at which hypertrophic arthritis tends to begin. It is difficult to see why atrophic arthritis should largely leave the stage at mid-life and why hypertrophic arthritis enters it then, unless these disease states reflect or represent in some way different age responses to the exciting factors. The influence of age as a determining factor in disease of those particular expressions which certain morbid proc-

esses or entities take, is illustrated by disease of the pituitary gland which in youth may express itself as gigantism and in the latter decades as acromegaly. Recent observations by Jaffe and Bodansky<sup>4</sup> have shown that in guinea pigs age determines the response of the animal to parathormone to such an extent that it is possible by means of injections of parathormone to produce osteitis fibrosa cystica in young animals but not at all in old ones. The expression which renal disease takes in the young offers some contrasts to that which is seen in older persons, and certain differences of the same order are to be observed in connection with cardio-vascular pathology. Again, diabetes in the young exhibits some differences as compared with the disease encountered in the more elderly, and much the same comment can be made regarding tuberculosis. It is thus clear that age introduces factors which may importantly condition the final expression of that deviation of physiology which may underlie any large syndrome, and it becomes pertinent to determine if possible the extent to which this is the case in the syndrome of arthritis. Apart from the clearer concept of the disease which would be afforded by observations elucidating this influence, certain definite and important therapeutic procedures would be given greater or less emphasis. If it could be shown that the surface phenomena of atrophic or hypertrophic arthritis are conditioned in part or largely by age, a wider outlook would have to be entertained upon the problem as a whole, and emphasis upon the separate identity of the two types would be more difficult of justification.

In view of the clear-cut results characteristic of hypertrophic arthritis which followed attempts at reproduction of some of the phenomena of arthritis by ligation of the blood supply to the patella of adult dogs, it seemed desirable to repeat these experiments making use of young dogs only. If it were shown that the response of the tissues differed markedly in young and old animals, the implication would be strong that age constitutes a decisive factor in the induction of hypertrophic arthritis. One starting point in the experiments to be cited was the observation that one of the dogs in the first series operated upon presented ununited epiphyses and that

this animal showed after operation less overgrowth of the patella than developed in the other and older dogs. Experiments were accordingly undertaken upon a series of five dogs, the results of which are set forth in the accompanying protocols. Of five experiments, only three were successful; two failed because of the death of the animal or other accident. In view, however, of the long time required to carry through experiments of this nature, in view of the many hazards to which very young dogs are subjected in the course of such experiments, and in view of the fact that upwards of a year must elapse before further data could be forthcoming, it seems justifi-



FIG. 1. Roentgen-Ray of Old Dog.

Normal patella of dog "Wooley".

Patella of dog "Wooley" six months after ligation of the blood supply to it. Note the size of the overgrowth.

able to present in the form of a preliminary report the results obtained to date.

Dog No. 6—"Collie".<sup>1</sup>

Dog No. 7—Male mongrel, wire-haired terrier, named "Wire-haired", seven months old, 15 pounds in weight, was operated upon November 4, 1929. The blood supply to the

gen-ray of February 22. Epiphyses are more nearly united.

July 25, 1930. The epiphyses are united; otherwise no change from the roentgen-ray of May 10. (Figure 2)

November 22, 1930. No change from the roentgen-ray of July 25. On November 22, the dog was sacrificed.

Examination after death showed a normal



FIG. 2. Roentgen-Rays of Young Dogs.

Normal patella of dog "Wire-haired".

Patella of dog "Wire-haired", eight and three-quarters months after ligation of its blood supply. Note absence of distal growth.

patella of the right leg was ligated, resulting in lameness of that leg. The lameness almost disappeared in one week.

Roentgen-rays of the leg operated upon on the following dates showed:

October 31, 1929. A normal knee joint, epiphyses not united. The roentgen-ray was taken before operation.

February 22, 1930. A slight change in the shape of the patella. The epiphyses are uniting.

May 10, 1930. No change from the roent-

left leg and patella and a right leg that seemed normal on dissection, had no thickening of the tissues nor adhesions, but that showed a slightly deformed articular surface of the patella. The right patella could be dissected and stripped as easily as a normal patella and it split with as much difficulty. It was smooth and shiny on its articular surface, but slightly livid in color. The sheath of the proximal tendon had grown somewhat down over the patella and up around its sides, almost merging with the articular sur-

face and covering an area of erosion on this articular surface. The patella showed no overgrowth, only a change in shape.

Dog No. 8—A female mongrel fox terrier, named "Pup", four months old, 10 pounds

in weight, was operated upon November 4, 1929. The blood supply to the patella of the right leg was ligated, resulting in lameness of that leg. The lameness almost entirely disappeared in one week. (Figures 3 and 4)

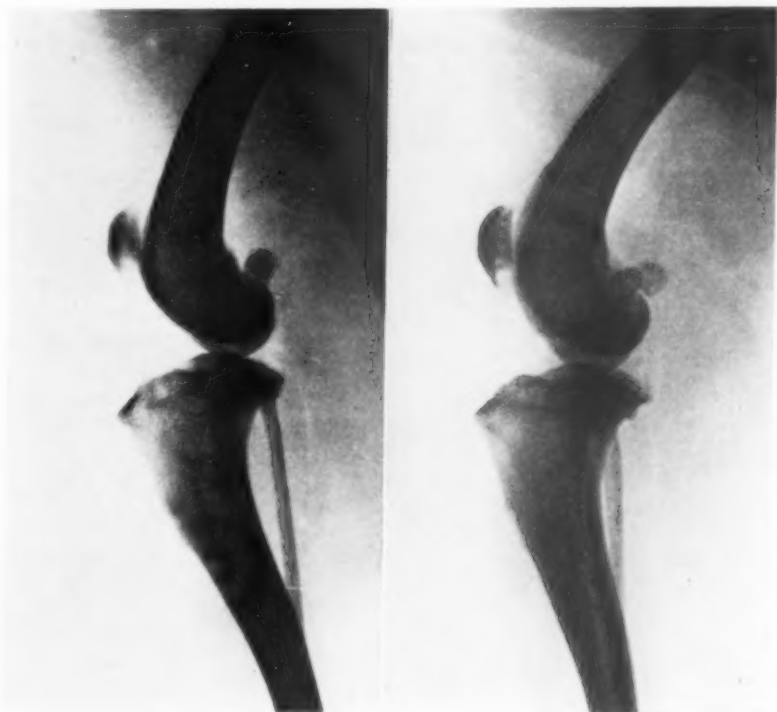


FIG. 3

Normal patella of dog "Pup".

Patella of dog "Pup" eight and three-quarters months after ligation of its blood supply. Note the spike-like but localized overgrowth distally.

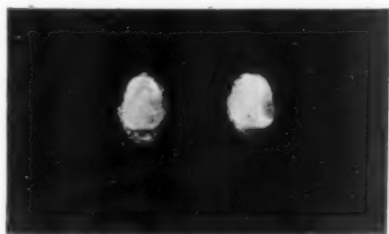


FIG. 4. Photograph of the patellae of dog "Pup" showing overgrowth of the patella on the left, twelve and one-half months after ligation of the blood supply to it. The overgrowth consisted of a spike rather than of the patella as a whole.

Roentgen-rays of the leg operated upon on the following dates showed:

October 31, 1929. A normal knee joint, epiphyses not united. The roentgen-ray was taken before operation.

February 22, 1930. A distal overgrowth, consisting of a spike from the outer edge of the patella.

May 10, 1930. A slight increase in the length of the spike distally, erosion of the patella making the spike appear longer.

July 25, 1930. No change from the roentgen-ray of May 10, except that the epiphyses are almost united.

November 22, 1930. No change from the roentgen-ray of July 25.

On November 22, 1930 the dog was sacrificed

Examination after death<sup>2</sup> showed a normal left leg and patella. The right leg dissected out normally; it showed no thickening of the tissues and only slight adhesions above the patella. There was, however, an area of erosion on the left side of the condyle of the femur at the knee joint. The right patel-

and giving the overgrowth a shelf-like appearance, and adding to its apparent length.

Dog No. 17—A female mongrel fox terrier, named "Cleo", five months of age, 15 pounds in weight, was operated upon September 1, 1931. The blood supply to the patella of the left leg was ligated, resulting in lameness of that leg. (Figures 5 and 6)

Roentgen-rays of the leg operated upon on the following dates showed:

July 26, 1931. A normal knee joint, epiph-



FIG. 5

Normal patella of dog "Cleo".

Patella of dog "Cleo" nine months after ligation of its blood supply. Note the very slight overgrowth distally.

la dissected out easily, but was slightly more difficult to strip than the normal one. The articular surface was smooth and glistening, but at least one millimeter shorter than the normal one. The right patella itself showed an overgrowth of about one millimeter, but only of the part of the patella that adhered to the tendon. There were areas of erosion under the articular surface of the patella, the one at the distal end being the largest

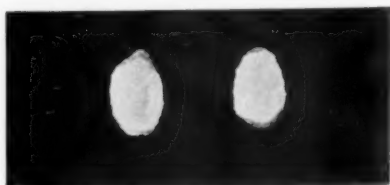


FIG. 6. Photograph of the patellae of dog "Cleo" showing overgrowth of the patella on the right, nine months after ligation of the blood supply to it.

yses not united. The roentgen-ray was taken before the operation.

October 24, 1931. No change from the roentgen-ray of July 26.

January 29, 1932. Epiphyses almost united, otherwise no change from the roentgen-ray of July 26, 1931.

February 8, 1932. No change from the roentgen-ray of January 29.

June 23, 1932. A very slight overgrowth distally, epiphyses united.

On July 8, 1932 the dog was sacrificed.

Examination after death showed a normal right leg and patella and a left leg that seemed normal on dissection, showed no tissue thickening and only slight adhesions around the patella. Both patellae were equally difficult to dissect free and strip. The left patella showed a slight overgrowth distally of the whole patella of about one millimeter (7 per cent). There were also places on the non-articular surface of the left patella that had remnants of suture material imbedded.

Dog No. 20—A female mongrel fox terrier, named "Spotty", three months of age, 8 pounds in weight, was operated upon February 19, 1932. The blood supply to the patella of the left leg was ligated, resulting in lameness of that leg.

Roentgen-rays of the leg operated upon on the following dates showed:

February 8, 1932. A normal knee joint, epiphyses not united. The roentgen-ray was taken before operation.

July 1, 1932 (after death). No change from the roentgen-ray of February 8.

On April 7, 1932, she died of an infection due to a cystic calculus.

Examination after death showed a normal right leg and patella, the epiphyses not united, and a left leg that dissected out easily, showing no tissue thickening and no adhesions around the patella. The left knee joint showed some discoloration due probably to hemorrhage following the operation; also its epiphyses were not yet united. The left patella showed no overgrowth. Both patellae split with slight difficulty and showed inside a brownish coloration of the bone, which was slightly larger in area in the normal patella. Both patellae stripped very easily.

A review of the above protocols shows that a difference apparently exists between the response of older dogs subjected to ligation of blood supply to the patella and that of younger animals chosen before union of the epiphyses. While some overgrowth of the patella may occur, in none of the three young dogs carried along for ten months or a year was there an overgrowth strictly comparable to that seen in all of the older animals; and in two of the young dogs the overgrowth was practically negligible or not to be detected at all.

It has been suspected by some students of arthritis that hypertrophic arthritis appears at mid-life because of the differing response of the tissues consequent upon some factor such as arteriosclerosis, or its vascular precursors, which is present in greater or less degree in all humans or animals that reach that age. In the three experiments just detailed there is a definite suggestion that prior to the appearance of the vascular or other changes of maturity, the end result falls short of the frank picture which is seen in the older animals.

The influence of age upon the type of arthritis cannot be regarded as settled on the basis of one line of experimentation, but one inference that may be drawn is that the phenomena of hypertrophic arthritis may represent a response due to the particular condition of the tissues rather than the effect produced by the action of any type-specific etiologic factor.

This general deduction must be correlated with the evidence that a number of factors often underlie both types of the disease, etiologically and therapeutic-

tically. As already mentioned, some of these factors in human beings are the influence of heredity, the bodily configuration, imbalance of the nervous system, a condition resembling vasoconstriction at the periphery, anatomical and physiological deviations of the gastrointestinal tract, and the influence of a balanced but restricted dietary.<sup>5,6</sup>

To this list might be added the influence of focal infection though some observers believe that infection has no relation to hypertrophic arthritis. Final proof of this is difficult, however; and it is probable that most dispassionate students regard focal infection as at least contributory to the syndrome of hypertrophic arthritis, although having less obvious and flagrant consequences than in atrophic arthritis.

To these considerations must be added the further fact that there is present in ossifying tissue, though only in

traces in unossified cartilage, the enzyme phosphoric esterase shown by Robison<sup>7</sup> to be concerned in the formation of bone.

#### SUMMARY

Preliminary report is made of experiments in which the attempt to produce hypertrophic arthritis in young dogs by curtailment of the blood supply to the patella is accompanied by slight or negative results as compared with similar attempts carried out upon mature animals. Taken in conjunction with other data the observations here cited seem, so far as they go, to add cogency to the view that hypertrophic arthritis is, in part at least, a function of the kind of response which the more adult tissues yield rather than exclusively a response to distinct etiologic factors basically different from those which are present in atrophic arthritis.

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# A Correlation of the Hemodynamics, Function, and Histologic Structure of the Kidney in Malignant Arterial Hypertension with Malignant Nephrosclerosis\*†

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THE correlation of the functional behavior and the structural characteristics of the blood vessels with the physiological units of the kidney is one of the most significant advances in the knowledge of kidney diseases during the past two decades. Evidence is accumulating that in the majority of instances of bilateral kidney disease of adult life the failure of the kidney function depends on a primary disease of the renal blood vessels. These cases are now variously classified as hypertensive renal disease, benign or malignant nephrosclerosis, and arteriosclerotic kidney disease. Contrariwise, in acute and chronic glomerulonephritis an "infectious process" is believed to involve primarily the glomeruli and tubules. The pathological state of the blood vessels in these latter cases, particularly in chronic glomerulonephritis, also plays a signifi-

cant rôle in the mechanism of disturbed kidney function.

In this rather simple but somewhat arbitrary grouping of bilateral kidney diseases, the classification of malignant nephrosclerosis is particularly difficult. Volhard and Fahr,<sup>1</sup> and Löhlein<sup>2</sup> separated this condition from the larger group of glomerulonephritis on the basis of the age of the patients, the rapidly fatal course, certain laboratory findings, and the "acute" histological changes in the glomeruli. The infectious character of the glomerular lesions was emphasized by Volhard and Fahr without sufficient consideration of the vascular lesions. Recently, through the efforts of Fahr,<sup>3</sup> the significance of the necrotizing arteriolitis, productive endarteritis and periarteritis of the kidneys and other organs has been receiving a new interpretation. He believes that the glomerular changes, which often predominate in the histologic picture, represent secondary effects of prolonged ischemia produced by vascular damage. Löhlein,<sup>2</sup> Jores,<sup>4</sup> Bell and Clawson,<sup>5</sup> and Shapiro<sup>6</sup> have claimed that the fundamental mechanism of benign and malignant nephro-

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sclerosis is of identical nature, and that these conditions differ only in the rate of their development. These authors believe that the more rapid decrease in the blood supply in malignant nephrosclerosis results in glomerular ischemia and in more acute histological changes resembling those of an infectious process. Stern,<sup>7</sup> Fishberg,<sup>8</sup> Murphy and Grill<sup>9</sup> also agree that both benign and malignant nephrosclerosis are due to vascular sclerosis.

Volhard<sup>10</sup> in 1923 relinquished his toxic theory of the etiology of malignant nephrosclerosis and attributed the histological changes to a general vasoconstriction associated with an intense capillary spasm of the glomeruli. According to him, the capillary ischemia thus caused tends to produce degenerative and proliferative changes. This concept was rejected recently by Klemperer and Otani,<sup>11</sup> who pointed out that if in the pathogenesis of this condition the capillary system were the seat of primary disturbance, the changes should be distal to the glomeruli, whereas in reality the vascular changes lie in the afferent arterioles as well as in the glomeruli. They traced the origin of the glomerular changes to thrombotic or proliferative occlusion at some point in the afferent arterioles. Meyer-Stettin,<sup>12</sup> Sternberg,<sup>13</sup> Ask-Upmark,<sup>14</sup> and others have, on the other hand, brought forward evidence against the identical sclerotic character of benign and malignant nephrosclerosis. It is evident, then, that at present a detailed interpretation of the changes in the blood vessels and in the kidney units in malignant nephrosclerosis is not possible.

An unusual coincidence of events,

to be described below, has permitted us to conduct observations on malignant nephrosclerosis which allow for the first time a correlation between the hemodynamics of renal circulation and the structure of the blood vessels and the function and structure of the kidney. Some data concerning the natural history of the disease have also been obtained. Below we present the clinical course of the disease as observed in a patient, followed by functional and histological studies.

#### I. CLINICAL COURSE

R. J. W., a 27-year-old male white truck driver, was admitted to the hospital November 16, 1930. His *chief complaint* was "blood in the urine". He was "in perfect health" until six months previously when he experienced hematuria, abdominal discomfort, and blurring of vision.

The hematuria occurred at first about every two weeks and lasted for about a day. These attacks gradually increased in frequency, intensity and duration until two months before entrance to the hospital. Since then hematuria had been continuous but with changing severity. No retention or incontinence of urine, chills, fever, or edema was observed. The abdominal discomfort was generalized, rather constant, and of mild degree. Heat, rubbing and simple medications did not relieve the pain. Blurring of vision was rather diffuse. In addition to these three main symptoms, he also suffered from headache, nausea, and vomiting, which were attributed by the patient to the consumption of alcohol. He had been a heavy drinker for the past three to four years. He claimed some correlation between alcoholic debauches and renal hemorrhages.

Dyspnea, experienced on moderate exertion, developed six months previous to admission. Periods of palpitation lasting 10 to 15 minutes had been occasionally observed. No other noteworthy changes in the function of organs were noticed.

The patient had suffered in the past from infrequent attacks of tonsillitis. The history

as to other infections was essentially negative with the exception of the occurrence of gonorrhea. His mental makeup was natural. No history of familial diseases was obtained.

Because of the free unilateral renal bleeding observed during cystoscopy, and because of certain changes in the roentgen-ray shadow of the kidney pelvis, a surgeon had been led to inform the patient of the possible existence of a malignant tumor of the left kidney. Following an attack of profuse

hematuria, the patient was rushed to the hospital for an immediate nephrectomy.

A left-sided nephrectomy under novocaine spinal anesthesia was performed November 18, 1930. The observations made during this operation will be reported further on.

The *physical examination* the day following the nephrectomy revealed a rather thin, ivory pale adult with prominent shiny eyes, comfortably lying flat in bed. The pupils reacted normally. The ocular fundi were



FIG. 1. Cortical surface of the left kidney removed surgically. Numerous small sub-surface hemorrhages are visible. X 1.3.

edematous with swelling of both discs and pronounced blurring of the margins. Numerous small, irregularly shaped, whitish areas were visible over both retinas. The small arteries were narrow and both these

any evidence of engorgement. The thyroid gland was not palpable. The superficial veins of the upper chest anteriorly were somewhat dilated. The lungs were normal. The apex beat of the heart in the fifth costal interspace was



FIG. 2. Surface of the longitudinal cross section of left kidney removed surgically. Scattered minute hemorrhagic areas. X 1.3.

and the small branches of the veins were tortuous. Arterial compression of the large veins was observed. The mucous membranes of the mouth were rather pale. The tonsils were small and innocent in appearance. No exudate could be squeezed out. The veins of the neck showed normal pulsations without

rather prominent. The maximal left diameter of the heart was only 10 cm. in the fifth interspace. The entire precordium was elevated through the force of the systolic impulse of the heart. The first heart sound was of normal intensity and quality and was continued by a short high-pitched systolic

murmur over the apex. The second sound over the apex was loud. At the base there was a reduplication of the second sound. The aortic second sound was metallic in character and loud. The heart rate was regular. The radial pulse was small, well sustained, and forceful. There was no evidence of arteriosclerosis. The arterial blood pressure was 185 mm. of mercury systolic and 120 mm. diastolic. The abdomen showed some resistance. No organs were palpable. There was a very slight cyanotic pallor of the nail beds of the fingers. The extremities, otherwise, were negative. The neurological examination revealed no abnormal signs. The rectal temperature was normal. The specific gravity of the urine was 1.008. The blood contained 3,330,000 red blood cells and 15,000 leukocytes per cu. mm. with 70 per cent hemoglobin. The diagnosis following operation was *malignant hypertension with nephrosclerosis*.

It is of interest that the first specimen of urine obtained following operation, contrary to the one obtained before, was free of blood. The chemistry of the blood and the kidney function tests, however, indicated for about two weeks after operation a progressive impairment of the kidney function. The urea clearance test reached as low a level as 3.4 c.c., or 6.4 per cent of the average normal clearance with a blood urea content of 142 mg. per 100 c.c.; and the creatinine clearance 8.1 c.c. of filtrate of urine with 11.6 mg. of creatinine in 100 c.c. of blood. Simultaneously with these changes the blood pressure rose to 200 mm. of mercury systolic and 130 mm. diastolic. The degree of edema of the retinal discs increased. Nausea and vomiting were occasionally present. The patient received a diet containing 20 gm. of protein with an adequate caloric content. The fluid intake was liberal. From the seventeenth day after the operation onward the kidney function showed progressive improvement and simultaneously the patient felt very much better. The appetite became voracious. The edema of the optic discs decreased. Toward the end of December his general condition was excellent and the blood urea fell as low as 47 mg. per 100 c.c. of blood.

Beginning soon thereafter, however, the blood pressure rose again to from 200 to 210

mm. of mercury systolic and 130 mm. diastolic. This was followed in four days by severe headaches, puffiness about the eyes and a decrease in the functional capacity of the kidney with unchanged urinary sediment. On January 8th headache was intense, and nausea and vomiting were also present. No explanation could be found for this attack of cerebral vascular crisis, which could not be relieved with luminal and pyramidon. The next day the manifestations of the cerebral crisis improved except for the facial edema. The following night a severe attack of cough and dyspnea developed. The patient sat up in distress and raised frothy blood-tinged sputum. This, together with the moist râles heard over the entire chest, suggested an attack of "paroxysmal nocturnal dyspnea" (cardiac asthma) with pulmonary edema. Morphine (gr. 1/4) and atropine (gr. 1/60) relieved this distress promptly, and in the morning the patient felt comfortable. There was, however, impaired resonance of mild degree over the right side of the chest anteriorly and posteriorly with somewhat decreased excursion of the diaphragm. The breath sounds were diminished and there was an increase in the spoken voice and fremitus. The arterial blood pressure was 200 mm. of mercury systolic and 130 mm. diastolic; the vital capacity of the lungs was 4200 c.c. The liver and spleen were not palpated and ascites and edema were not observed.

In the evening of January 11th we had another opportunity to observe in detail the development of paroxysmal nocturnal dyspnea. The patient ate a good supper and was comfortable. At about 8 p.m. he felt a tight sensation beneath the manubrium sterni. He became restless and complained of inspiratory difficulty. The right side of the thorax now showed limited excursion with a few fine and medium consonating râles over that side. The arterial blood pressure was 205 mm. of mercury systolic and 136 mm. diastolic, the venous blood pressure 12 cm. of water. The condition grew rapidly worse. The patient was pale and cold and covered with sweat. The "tightness in the chest" and the dyspnea became so severe that a marked degree of orthopnea developed. There was extreme apprehension of death. The pa-

tient coughed with considerable distress, raising red frothy sputum with occasional red streaks of blood. The heart sounds became rapid, and while before the attack the aortic second sound was loud and metallic, now the relationship changed and the pulmonary second sound became accentuated and louder than the aortic second sound. There was at the same time an almost complete fixation of the right side of the thorax with dullness and a definite increase in the intercostal retraction. The breath sounds were almost completely absent but numerous fine, medium and coarse râles were heard throughout the right lung. *While these physical signs indicated severe changes in the right lung, the physical signs of the left side of the chest remained essentially normal.* The heart rate rose to 150 per minute. The arterial blood pressure was 225 mm. of mercury systolic and 140 mm. diastolic.

Morphine (gr. 1/4) failed to give any relief. Blood pressure cuffs were then applied on the proximal end of the four extremities and the pressure was raised in each to the level of the diastolic blood pressure. Within one minute after the application of venous stasis the dyspnea, cough, and raising of sputum disappeared and the patient fell asleep. On relieving the pressure in the cuffs temporarily at ten-minute intervals, all the symptoms and signs returned though with decreasing intensity. After one hour the cuffs were removed and the patient remained comfortable. Physical examination now was essentially the same as before the attack. The loud metallic quality of the aortic second sound returned and the accentuation of the pulmonary second sound subsided. The patient was given tincture of digitalis in an amount equivalent to 2 minims per pound of body weight. Next day the patient was comfortable. The breath sounds were somewhat reduced over the right side. A few days later the patient suffered again from a similar attack of paroxysmal dyspnea. Between attacks, Cheyne-Stokes' type of breathing developed, with a sense of suffocation toward the end of the apneic stage. Intravenous administration, slowly, of 50 per cent glucose solution gave considerable relief for six hours. Ten days after the first attack of dyspnea, or on January 19th, the

patient appeared exhausted, and involuntary jerky movements of the extremities developed; Cheyne-Stokes' breathing was now marked with prolonged apnea and a protodiastolic gallop rhythm appeared. The pulmonary second sound became persistently louder than the aortic second sound. Râles were heard over the chest. The liver edge was 6 cm. below the costal margin. In order to relieve the manifestations of uremia a lumbar puncture was performed. The spinal fluid pressure was 280 to 320 mm. of water. The dynamics and oscillations of the fluid were normal. The intraspinal injection of 20 c.c. of a 10 per cent magnesium sulfate solution caused a temporary drop of fluid pressure to 200 followed by a rise to 280 mm. of water. Inhalation of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen gave relief from the irregular periodic breathing. The patient during the following two days became more drowsy. There was increasing edema of the eyegrounds and the veins of the discs were more congested. A pericardial friction rub appeared. The blood pressure was 190 mm. of mercury systolic and 120 mm. diastolic, the pulse 130 per minute. The spinal fluid pressure January 19th was 350 mm. of water with normal dynamics. On January 20th the patient was very stuporous. The pulmonary edema disappeared although the general condition grew worse. On January 22nd the pericardial friction rub persisted. He was now growing weaker, although the blood pressure was still maintained as high as 180 mm. of mercury systolic and 120 mm. diastolic. The pulse was 136 per minute. Next day he was comatose, the blood pressure was 175 mm. of mercury systolic and 100 mm. diastolic, pulse 136. He died January 24th.

Obviously the left kidney of this patient was removed because of a mistaken diagnosis and because of the alarming unilateral renal bleeding. Considering that the patient had experienced six months previous to his admission such symptoms as hematuria, abdominal discomfort and blurring of vision, and considering that he lived two months after the operation, it may

be concluded that the course of this rapidly fatal disease was not significantly shortened in his case by the nephrectomy.

Attacks of paroxysmal dyspnea, such as this patient experienced, are not rare in malignant hypertension. They develop often independently of the kidney involvement, usually at an early stage of relative failure of the left ventricle. One of us (S.W.) has observed attacks of paroxysmal dyspnea in a child eight years old with malignant hypertension who died as a result of heart failure while still retaining normal kidney function. The changes in the clinical symptoms and signs which occurred during attacks in the case recorded in detail above, have been observed by us in a number of other similar cases. They depend on the circulatory changes, which, together with therapeutic measures in this syndrome, have been previously summarized.<sup>15</sup>

## II. FUNCTIONAL STUDIES

*The Hemodynamics of the Normal Kidney and of the Kidney with Malignant Nephrosclerosis.* If the human kidney is exposed surgically, blood from the renal vein can be obtained easily under sterile conditions and with apparent safety. In puncturing the vein it is essential that no more than gentle traction be made upon the kidney, so as not to interfere with the normal free flow of the blood. We have punctured the renal vein in five cases without any resultant bleeding. The composition of the arterial blood throughout the body is identical so that if simultaneously with obtaining blood from the renal vein blood is collected from the femoral artery and the specimens studied chemically, information

can be obtained concerning the blood flow through the kidneys. Table 1 presents the results of such observations on the oxygen and carbon dioxide content of the blood, obtained under oil, from the patient with malignant hypertension and nephrosclerosis and from three individuals with normal kidney function who had one kidney exposed for surgical suspension. The 10 to 20 c.c. of renal vein blood were drawn slowly during a period of from two to three minutes so as to represent a sample of a relatively large amount of blood flowing through the kidney. In addition to obtaining blood from an artery and from the renal vein, blood was also obtained from the femoral vein in order to form a comparative estimate of the blood flow through the kidney and through a lower extremity. In order to ascertain whether or not spinal anesthesia exerts an influence on the blood flow, in two of the control cases and in the patient with nephrosclerosis, blood was obtained from the femoral vein during anesthesia and again after the effect of the anesthetic wore off. Obviously if the metabolism of an organ remains unaltered or becomes increased, a decreased oxygen difference between the arterial and venous blood indicates an increased blood flow. The data given in table 1 demonstrate that the oxygen difference between the bloods obtained from the femoral arteries and veins with and without anesthesia was essentially unaltered in the patient with hypertension, while it was increased definitely in one, and essentially unaltered in the second control "normal" cases. The arterial blood pressure was distinctly lower during the spinal anesthesia in the patient with nephrosclerosis, but it

TABLE I  
BLOOD GAS STUDIES OF THE KIDNEY AND LEG IN THE CASE OF MALIGNANT NEPHROSCLEROSIS COMPARED WITH NORMAL SUBJECTS

Name	Age	Condition of Kidneys	Arterial Blood Pressure		Heart Rate	Femoral Artery				Femoral Vein		Renal Vein		Femoral Arter.-Ven. Difference		Renal Arter.-Ven. Difference		Remarks
			Syst.	Diast.		O <sub>2</sub> Content	O <sub>2</sub> Capacity	O <sub>2</sub> Saturation	O <sub>2</sub> Content	CO <sub>2</sub> Content	Vol. %	O <sub>2</sub> Content	CO <sub>2</sub> Content	O <sub>2</sub>	CO <sub>2</sub>	O <sub>2</sub>	CO <sub>2</sub>	
			mm. Hg	mm. Hg	per min.	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	Vol. %	
R.W.	27	Malignant Nephrosclerosis, impaired	220	130	108	10.58	12.01	88	52.12	5.98	56.76	—	—	4.60	4.64	—	—	Before spinal anesthesia
R.W.	27	Malignant Nephrosclerosis, impaired	110-140	75-100	88	11.17	11.97	93	49.16	7.72	53.46	11.32	50.45	4.45	4.30	-0.15	1.29	During spinal anesthesia
A.B.	47	Normal	115	70	68	—	—	—	—	14.29	53.92	—	—	4.93*	6.26*	—	—	Before spinal anesthesia
A.B.	47	Normal	120	85	68	19.21	20.04	96	47.66	14.41	54.83	16.34	50.45	4.80	7.17	2.87	2.79	During spinal anesthesia
R.B.	45	Normal	120	60	80	18.20	18.84	—	46.20	12.14	52.28	—	—	6.06	6.08	—	—	Before spinal anesthesia
R.B.	45	Normal	105	62	75	18.46	19.00	—	45.00	14.60	49.90	15.50	49.28	3.86	3.90	2.96	4.28	During spinal anesthesia
D.K.	40	Normal	110	60	78	16.25	16.79	97	37.14	8.93	43.93	14.96	42.03	7.32	6.79	1.29	4.89	During spinal anesthesia

\*Assuming that the gaseous content of the blood from the femoral artery is the same before and during spinal anesthesia.

did not change appreciably in the control cases. The most significant observation is, however, the low oxygen difference between the blood from the renal artery and vein in the control cases. This, in view of the fact that the metabolism of the kidney as compared with other organs is high, corresponding to 8.2 per cent of the total energy consumption in rats, and 7.9 per cent in dogs,<sup>16,21</sup> conclusively indicates the existence of a rapid blood flow through the kidney. The average oxygen difference between the arterial and venous blood of the kidneys of the control subjects was 2.37 vol. per cent. The arterial blood, therefore, lost an average of 13 per cent of its oxygen content during its passage through the kidney. Rhoads, Van Slyke, Hiller and Alving<sup>17</sup> reported that the proportion of oxygen removed from the blood by the kidney of the dog was 10 to 20 per cent of the arterial oxygen content. This indicates a fair degree of agreement between the rapid blood flow through the kidney of the dog and of man. In all three normal kidneys the arteriovenous oxygen difference was distinctly less in the kidney than in the lower extremities.

In the case of the patient with ne-

phrosclerosis, there was no apparent utilization of oxygen by the kidney. On the contrary, the oxygen content of the blood obtained from the renal vein was slightly higher. This surprising finding of somewhat higher blood oxygen content in the renal vein cannot be attributed to technical error in the analysis. This belief is supported by the finding of a higher oxygen capacity of the venous blood (12.66 vol. per cent) than of the arterial blood of the kidney (11.97 vol. per cent). Our interpretation is that the rate of blood flow through the kidney in this case was unusually great, even when compared with the relatively rapid renal blood flow in the control cases with normal vascular systems and normal arterial pressures. The slight increase in the oxygen capacity of the blood in the renal vein was probably due to an increased hemoglobin concentration produced by the loss of water content of the blood in its passage of glomerular capillaries. That the data (table 2) were obtained while the kidney was functioning is supported by the fact that the urea and creatinine clearance tests during spinal anesthesia in the control case were essentially normal. In the case of nephrosclerosis these

TABLE II  
A COMPARISON OF CHEMICAL CONSTITUENTS OF THE RENAL ARTERIAL AND VENOUS BLOOD IN THE CASE OF MALIGNANT NEPHROSCLEROSIS AND IN A CONTROL SUBJECT

Condition	Source of Blood Specimen	Non-Protein-Nitrogen	Urea Nitrogen	Creatinine	Chlorides
		mg./100 c.c.	mg./100 c.c.	mg./100 c.c.	mg./100 c.c.
(Malignant Nephrosclerosis)	Kidney artery	66	36.1	5.2	590
	Kidney vein	58	32.5	4.9	597
(Control)	Kidney artery	—	13.0	1.4	605
	Kidney vein	—	10.0	1.3	611

tests were about the same as the tests obtained five days later under entirely natural conditions (table 3).

The average 2.4 vol. per cent oxygen difference between the blood of the renal artery and vein observed in the three control cases is smaller than that observed in other organs studied in man. Weiss and Lennox observed an oxygen difference of 7.1 vol. per cent between the blood of the cubital arteries and veins of the arm, and in a study of the brain they noted an average difference of 6.2 vol. per cent between the blood of the internal carotid artery and the internal jugular vein.<sup>18</sup> In the leg, Weiss and Ellis observed an oxygen difference of 4.1 vol. per cent between the blood of the femoral artery and vein.<sup>19</sup> In the heart there has been found 5.3 vol. per cent difference between the arterial and venous blood of the ventricles.<sup>20</sup>

*The Chemical Composition of the Arterial and Venous Blood of the Kidney.* Table 3 presents data concerning the comparative content of certain constituents of the arterial and venous blood of the kidney. The differences of the values between the arterial and venous blood are exceedingly small. In view of the unusually rapid blood flow through the kidney, such a small loss of waste products during the passage of blood is not surprising. The amount of the chemical substances in the venous blood, with the exception of chlorides, was less than in the arterial blood, although at times the differences fell within the error of the analysis.

Dunn, Kay and Sheehan<sup>23</sup> observed in rabbits that each 100 c.c. of blood containing originally 30.2 mg. of urea

TABLE III  
THE UREA AND CREATININE CLEARANCE DURING SPINAL ANESTHESIA IN THE CASE OF MALIGNANT NEPHROSCLEROSIS AND IN A CONTROL SUBJECT

Age	Diagnosis	Heart Rate per min.	Arterial Blood Pressure		Blood Urea Nitrogen mg./100 c.c.	Urine Urea Nitrogen mg./100 c.c.	Urea Clearance		Blood Creatinine mg./100 c.c.	Urine Creatinine mg./100 c.c.	Glomerular Filtrate	Remarks
			mm. Hg	mm. Hg			c.c.	Per cent Normal				
27	Malignant nephrosclerosis	108	110-140	75-100	35.1	344	11	20	5.2	72	19.5	Duration of tests 95' Left nephrectomy
40	Floating kidney	78	110	60	13.0	772	60	111	1.4	103	71.3	Duration of tests 77' Right nephropexy

lost 2.5 mg. in passing through the kidney. Their study, performed under more ideal experimental conditions, is in harmony with our findings in man. It is, however, contrary to the earlier observations of Picard<sup>24</sup> in dogs that the urea content of the blood from the renal vein was half that of the blood from the artery. Picard's findings would suggest a blood flow through the human kidney of 150 c.c. per minute, a figure undoubtedly low. Sheehan's recent finding<sup>22</sup> in the rabbit would suggest an average corresponding blood flow of 750 c.c. per minute through the kidneys in man which, even if high, is probably close to the actual state of affairs. As the combined weight of the two kidneys in man is only 1 to 240 in proportion to the body weight, the blood flow through the kidney must be great when compared with other organs.

*The Secretory Function of the Kidneys.* Table 2 presents the urea clearance tests of the kidneys during surgical operation under spinal anesthesia. In the control case, the urea clearance test measured according to the method of Van Slyke was normal. The creatinine clearance was somewhat below the average normal value.

In the case of nephrosclerosis the urea clearance test during operation was 20 per cent of normal. The longer part of this clearance test fell within the period directly after nephrectomy; and since the clearance test five days later showed 13 per cent of normal, the kidneys during the surgical procedure under spinal anesthesia may be regarded as functioning adequately. Table 4 presents the urea and creatinine clearance tests of the right kidney after removal of the left one. During the three months of observation, we

performed on this patient 12 urea clearance tests according to the Van Slyke method,<sup>25</sup> and 11 creatinine clearance tests according to Rehberg's method.<sup>26</sup> The results of these two tests paralleled each other fairly closely. It is of interest that, in accordance with the history of the case, these tests indicated considerable fluctuations in the functional capacity of the kidney during the period of three months. Following operation the urea nitrogen content of the blood rose from 35 to 143 mg. per 100 c.c. of blood as the clearance dropped from 20 to 6 per cent of the normal. Simultaneously the blood creatinine rose because the glomerular filtrate decreased. With the subsequent improvement in the kidney function the urea clearance rose to 12 per cent, and the creatinine clearance to 15 per cent of the normal value. Following this temporary improvement, the kidney function showed further impairment. When the urea clearance reached about 3 per cent, and the creatinine clearance about 5 per cent of the normal values, clinical manifestations of uremia developed.

*Concentration Dilution Tests of Kidney Function.* On two occasions, a concentration dilution test was performed on the patient with nephrosclerosis by the method described.<sup>27</sup> In order to study the concentration power of the kidney more specifically, in addition to the specific gravity of the urine, the creatinine concentration of the blood and urine were also measured. These data allow the calculation of the concentration index between the blood and the glomerular filtrate. The results of one of these tests are presented in table 5. Obviously the water elimination, as well as the concentra-

TABLE IV  
THE UREA AND CREATININE CLEARANCE IN THE CASE OF MALIGNANT NEPHROSCLEROSIS  
FOLLOWING LEFT NEPHRECTOMY

Date	Blood Pressure		Heart Rate	Blood Urea Nitrogen	Urea Clearance		Blood Creatinine	Creatinine Clearance
	Syst.	Diast.			c.c.	per cent normal		
	mm.Hg	mm.Hg	per min.	mg./100 c.c.			mg./100 c.c.	c.c. filtrate
1930								
Nov. 20	150	104	116					
Nov. 21	175	105						
Nov. 22	165	125	100					
Nov. 24	175	125	96	83.7	13	17	6.6	10
					5	9		
Nov. 25	185	130	100					
Nov. 27	185	130	84					
Nov. 28	180	120	80	142.7	3	6	10.4	8
					4	7		9
Nov. 29	185	120	80					
Dec. 1	190	130	76	141.5	3	6	11.6	7.3
					3	6		8.9
Dec. 2	185	125	76					
Dec. 3	185	115	84					
Dec. 4	190	110	80					
Dec. 5	180	110	76	119.6	5	9		
					6	8	10.4	10.8
								9.3
Dec. 6	185	105	76	83.6	6	8	8.3	8.5
					7	9.4		9.1
Dec. 16	165	110	90	66.9	9	11.4	7.5	15.0
					8	11		13.0
Dec. 20	180	106	100					
Dec. 23	180	115	108	52.3	9	12	6.7	14.6
					8	10.5	6.7	14.5
Dec. 27	175	115	96					
Dec. 30	190	125	92	47.3	6	11		
					8	11.2		
1931								
Jan. 2	200	130	96					
Jan. 6	210	130	100	56.0	4	8.5		
					5	10	7.3	14.5
								12.6
Jan. 8	205	140	100					
Jan. 12	185	110	121	52.0	4	8.5	8.4	6.8
Jan. 14	185	100	120	80.9	3	6.5	12.8	5.1
								3.3
Jan. 15	175	100	120					
Jan. 19				116.1	1	2.4	15.4	5.6
					2	3.5		3.6
Jan. 23				145.0			18.5	

tion capacity of the kidney was seriously impaired. Notwithstanding the ingestion of a large amount of water, the water elimination showed only slight variations. The creatinine concentration index varied between 2.8

and 6.8, while in control subjects under identical conditions it usually reached the levels between 200 and 300. The results of this test indicate that in this case of malignant hypertension with nephrosclerosis both the volume

and the concentration of urine were fixed.

*Urinary Sediment.* The urinary sediment was studied daily. The most significant observations were the sudden variations from time to time in the number of white and red blood cells as well as in the character of the casts. A sediment with hyaline or granular casts and normal elements changed rapidly within a day or so to a sedi-

*Microscopic Examination:* There were foci of increased connective tissue infiltrated with many lymphocytes, some plasma cells and large mononuclears. In places, fairly numerous polymorphonuclear neutrophils were present. In such areas of sclerosis the tubules were narrowed. Scattered through the pyramids were numerous foci of hemorrhage, apparently capillary in origin. The glomeruli showed varying degrees of involvement. Some of them were normal, others showed acute lesions and still others more chronic changes. The acute lesions appeared

TABLE V  
THE CONCENTRATION-DILUTION AND CREATININE CONCENTRATION INDEX TESTS IN THE  
CASE OF MALIGNANT NEPHROSCLEROSIS

Time Interval of Specimen	Urine Volume	Specific Gravity	Urine Creatinine	Blood-Urine Creatinine Concentration Index	Glomerular Filtrate
	c.c.		mg./100 c.c.		c.c./min.
Jan. 1, 8:00 P.M.—	1600	1.008	44.6	4.4	10.6
Jan. 2, 7:00 A.M.					
7:00 A.M.—8:00 A.M.	95	1.010	48.1	4.8	7.6
8:00 A.M.—9:00 A.M.	50	1.011	50.0	5.0	4.0
9:00 A.M.—10:00 A.M.	170	1.007	27.8	2.8	7.8
10:00 A.M.—11:00 A.M.	130	1.007	29.2	2.9	6.4
11:00 A.M.—1:00 P.M.	200	1.009	49.5	4.9	8.3
1:00 P.M.—3:05 P.M.	170	1.009	65.4	6.5	9.1
3:05 P.M.—6:00 P.M.	200	1.011	68.0	6.8	7.5
6:00 P.M.—8:00 P.M.	165	1.011	62.1	6.2	8.7
8:00 P.M.—					
Jan. 3, 8:00 A.M.	1100	1.009	59.2	5.9	8.9

ment rich in red and white blood cells and casts containing red cells. The albumin content of the urine changed from a small to a heavy trace as the disease progressed.

### III. STRUCTURAL STUDIES

The kidney removed at operation appeared as follows:

*Gross Description:* The kidney weighed 213 gm. The capsule stripped easily. The cortex averaged 5.5 mm. in thickness. The cortical tissue was yellowish grey with a waxy texture. The pyramids in the upper pole showed evidence of small hemorrhages. Several of the pyramids had pearly white, diffuse, firm areas in the region of the kidney pelvis. The entire organ appeared to be edematous.

in various forms. The most common was a hyaline droplet degeneration of the tuft and, to some extent, also of the capsular epithelium, associated with a marked proliferation of the epithelium, especially of the capsule. In some instances this lesion involved the whole tuft with obliteration of the capsular space; in others it affected only a portion of the tuft.

The majority of the tufts in these lesions, when stained with Mallory's anilin blue stain (Lee Brown modification),<sup>28,29</sup> showed a meshwork of intracapillary fibers described by McGregor<sup>30</sup> as characteristic of glomerulonephritis. When only a portion of the tuft epithelium was involved, only the loops adjacent to this area showed such changes, the other loops remaining normal (figure 13). Other glomeruli showed necrosis with fibrin formation and infiltration of varying

numbers of polymorphonuclear leukocytes. A less frequent type of lesion was a necrotizing arteriosclerosis with an associated involvement of the glomerulus, accompanied by an infiltration of a considerable number of polymorphonuclear neutrophils. The more chronic changes in the glomeruli consisted

tained hyaline and granular casts and in places masses of red blood corpuscles and also numerous polymorphonuclear neutrophils and some large mononuclears. In view of the large number of leukocytes in the tubules the sections were carefully examined for organisms but none were found.

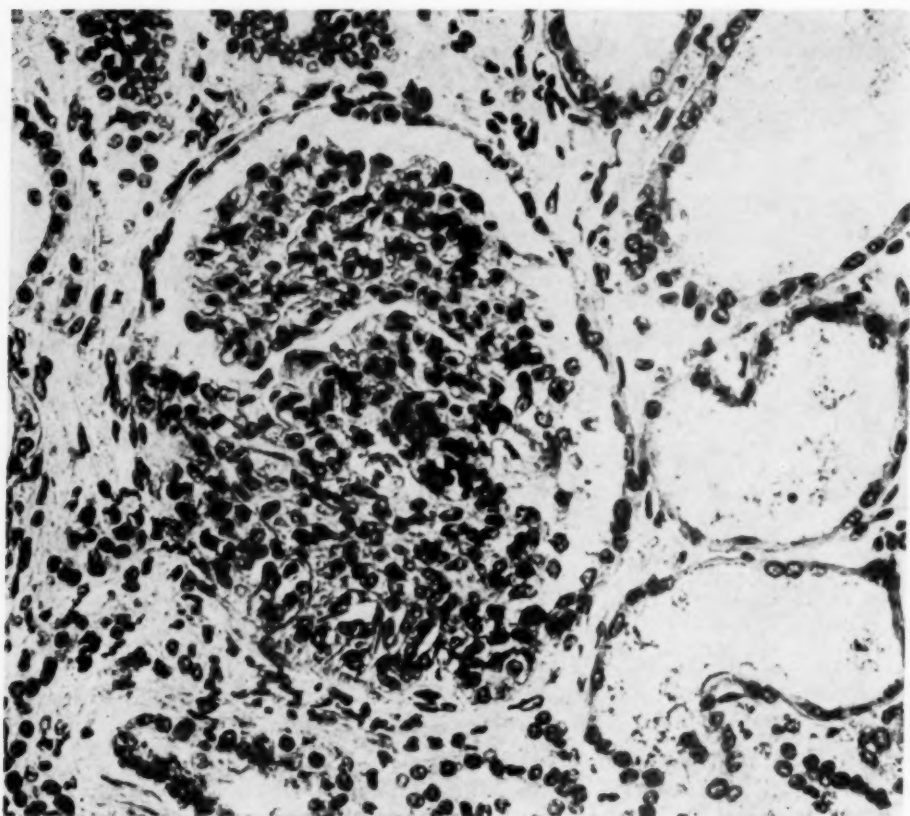


FIG. 13. Right kidney. Glomerulus showing focal lesion with localized reaction on part of epithelium. X 300.

of diminution in size with thickening and wrinkling of the basement membrane, described by McGregor as characteristic of hypertension.<sup>31</sup> Other glomeruli showed adhesions between the tuft and capsule, and still others were completely sclerosed.

The tubules in the areas showing fibrosis appeared atrophic. Elsewhere the cells of some of them contained hyaline droplets in their cytoplasm; in others the cytoplasm was more granular than normal. The tubules con-

The larger blood vessels showed no pathological changes. Many of the medium-sized and small arteries showed marked fibrous thickening of their walls. Numerous arterioles had thickened, hyaline walls. Some of the smaller arteries and arterioles showed widening of their lumens and necrosis, occasionally with hemorrhage into the surrounding tissue. Fat, demonstrated by staining, occurred especially in the atrophic tubules but was also present in non-atrophic tubules,

artery walls, and glomerular epithelium. Fat also occurred in the casts.

#### NECROPSY

*Gross Description.* The autopsy was performed two hours after death by Dr. J. B. Hazard. Only the essential findings are given below.

in thickness. The auricles and the right ventricle were markedly dilated, the ventricle being 0.25 cm. thick. The muscularis was pale red, and of firm consistency with no gross areas of scarring. The endocardium was smooth and all valves were negative. Lungs: Both lungs were enlarged and heavy. Section of the lungs revealed a firm, dark,

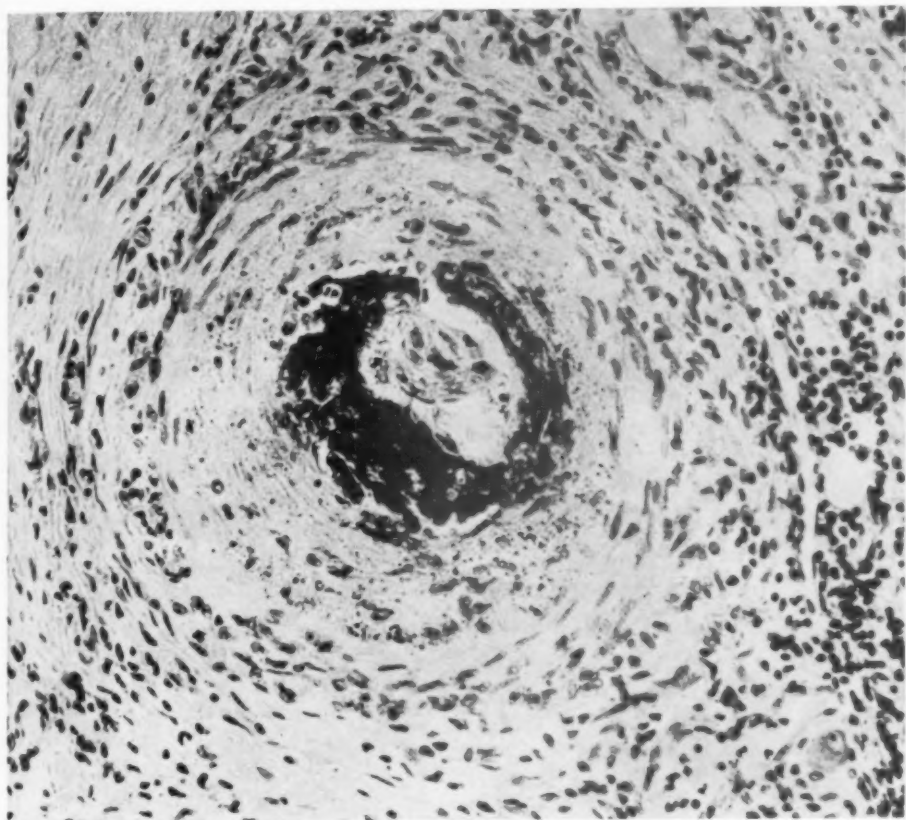


FIG. 15. Pancreas. Artery containing organizing thrombus. Wall degenerating and containing nuclear debris. X 250.

**Pleural Cavities:** There were about 500 c.c. of clear fluid in the right pleural cavity and 200 c.c. in the left. The surfaces of the cavities were smooth and glistening. **Pericardial Cavity:** Both parietal and visceral pericardial surfaces were covered with a layer of fibrin. About 150 c.c. of clear amber fluid were in the cavity. **Heart:** Weighed 690 gm. The wall of the left ventricle showed marked hypertrophy and measured 2.1 cm.

reddish grey tissue composing all lobes. A quantity of froth and dark red fluid could be expressed. **Liver:** Weight 1930 gm. Section revealed a dark brown tissue of soft consistency with a fine red mottling.

**Kidneys:** Left kidney was absent. The right kidney weighed 165 gm. The capsule stripped with moderate ease, leaving an irregular pale surface, speckled with many pin point, dark red spots. The cut surface

was pale pink and of soft consistency. In the cortex were several small irregular, red areas measuring up to 0.1 cm. in diameter. The cortex was uniformly thinned, measuring 0.4 cm. in thickness. The pyramids were not remarkable save for their pale color. The pelvis was negative. There was no dilatation of the ureter.

was old and was in the stage of organization. In places the organization process was beginning, in others it was advanced, or complete. This process was taking place, not only in the alveoli but also in the atria and bronchioles. Elsewhere the alveoli were normal or distinctly dilated. The blood vessels appeared normal. Spleen: The germ-



FIG. 3. Cortical surface of the right kidney at necropsy. Numerous small hemorrhages. X 1.3.

**Aorta:** It appeared smooth and yellowish white throughout. The elasticity was good.

**Microscopic Examination.** **Heart:** The muscle fibers were increased in thickness. There was a certain amount of lipomatosis and rarely a large mononuclear and mast cell in the connective tissue. The blood vessels appeared normal. The pericardium showed an acute fibrinous pericarditis. **Lungs:** The alveoli contained red blood cells, fibrin, and some large mononuclears. The fibrin

inal centers were not prominent and were inactive. A few contained a hyaline fibrinoid material. The central arteries showed a hyaline thickening of their walls; rarely, there was an infiltration of large mononuclear cells in the wall. The pulp contained numerous polymorphonuclear neutrophils, a considerable number of plasma cells, and a rare megakaryocyte. **Pancreas:** Many of the glands were dilated and contained a pink-staining material, often concentrically arranged, sug-

gesting concretions. In addition, many glands contained polymorphonuclear neutrophils in their lumens. There was an occasional necrotic acinus invaded by polymorphonuclear leukocytes. The connective tissue stroma was diffusely infiltrated with polymorphonuclear neutrophils, lymphocytes and large mononuclears. A considerable number of

sis as evidenced by loss of liver cells and sclerosis. In addition, an active, acute central necrosis, in places hemorrhagic in type, was present. An occasional arteriole in the portal areas showed hyaline in its wall.

Right Kidney: There was a marked increase in connective tissue with a moderate infiltration with lymphocytes; these cells



FIG. 4. Surface of the longitudinal cross section of the right kidney at necropsy. Numerous small hemorrhages. X 1.3.

the small arteries and arterioles showed a thickening of their walls, often with a deposit of hyaline. Occasionally one showed necrosis of its thickened wall. Several small arteries contained thrombi partially occluding their lumens. In one such artery (figure 15) the thrombus was undergoing organization while the vessel wall showed necrosis and hemorrhage. Rarely the thickened vessel wall contained fat.

Liver: There was a healed central necro-

were, however, much less numerous than in the kidney removed surgically. The glomeruli showed lesions of both an acute and more chronic nature. There was a considerable number of normal glomeruli. The number of glomeruli showing thickened and wrinkled basement membranes was considerably increased over that in the left kidney removed two months before. The acute changes in part resembled those in the first kidney. They consisted in hyaline droplet degenera-

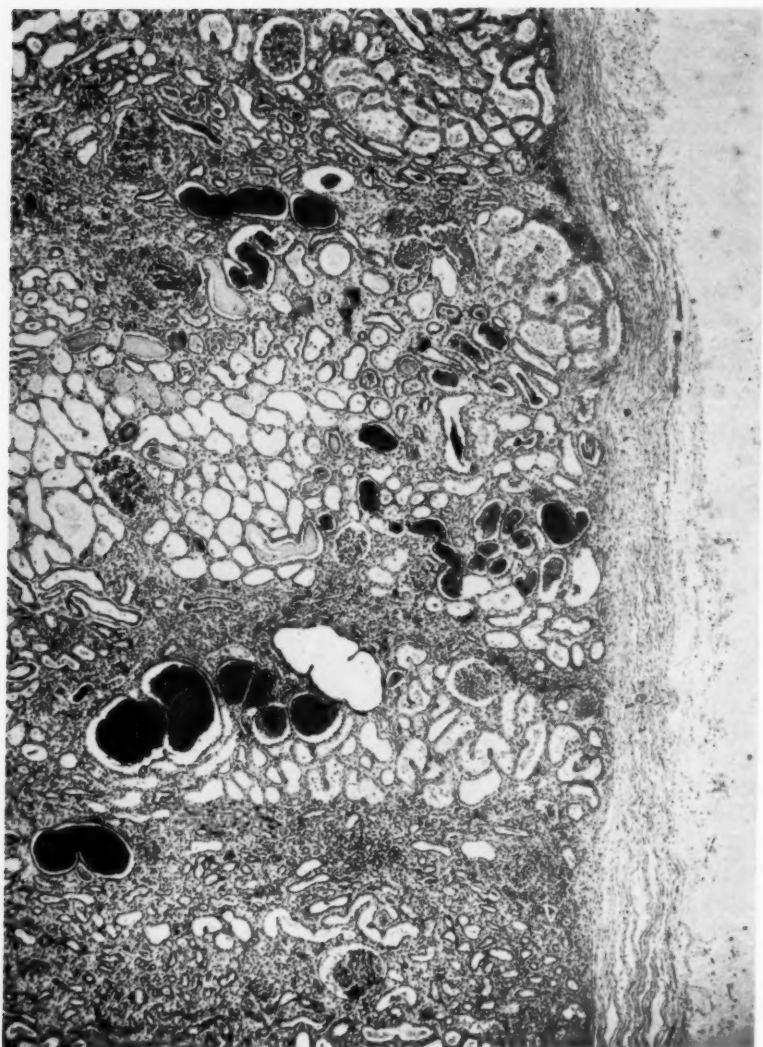


FIG. 8. Cortex of right kidney. Showing dilated tubules as contrasted with the left kidney. X 40.

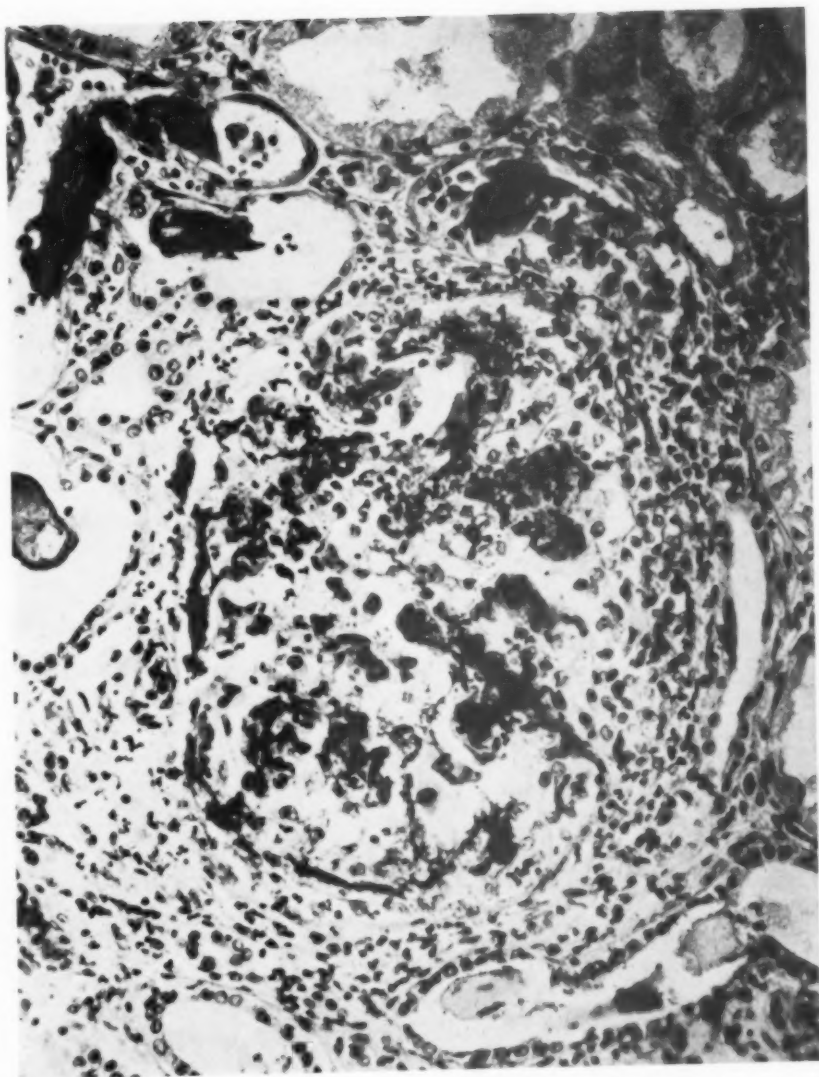


FIG. 9. Right kidney. Necrosis of glomerulus with some fibrin formation and infiltration of polymorphonuclear neutrophiles in and around the glomerulus. X 250.

tion of the tuft epithelium, often associated with marked proliferation of the capsular epithelium, with fusion between the tuft and capsular epithelium. As in the first kidney, the lesion sometimes involved the whole tuft and sometimes only a portion of it. The tufts themselves showed the same changes

the majority of these tubules contained only granular material, some had hyaline casts and others red blood corpuscles in their lumens. Similar groups of dilated tubules were found deeper in the cortex but here their number was considerably smaller. Hyaline droplets in the cytoplasm of the tubu-

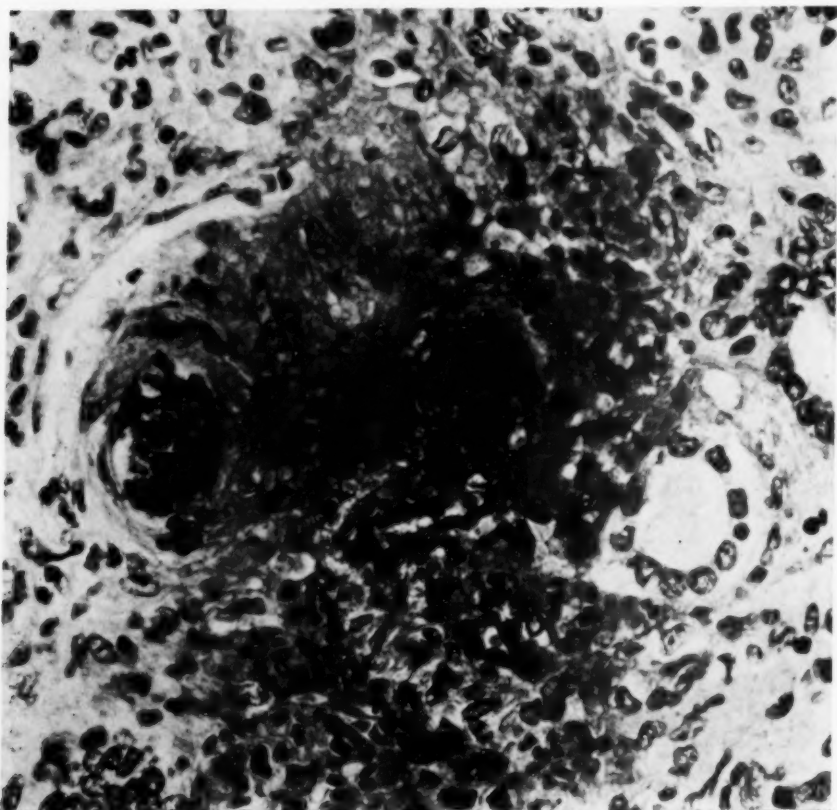


FIG. 10. Right kidney. Arteriolar hemorrhage. One vessel is cut longitudinally and can be followed into the hemorrhage. X 360.

described in the first kidney. In addition, there were some lesions of a more fulminating character. Such lesions consisted in necrosis of the arteriolar wall with necrosis and hemorrhage into the tuft and an infiltration of polymorphonuclear leukocytes, the lesion being essentially an infarct. In such glomeruli, there was associated capsular proliferation. Groups of tubules in the cortex under the capsule were dilated and their epithelium tended to be flattened. While

lar epithelium were quite common. In the sclerosed areas, the tubules were narrowed and collapsed. A few tubules contained polymorphonuclear leukocytes and in some of the collecting tubules in the pyramids there were hyaline casts and casts whose structure and staining reaction resembled hemoglobin. The blood vessel changes were essentially the same as in the other kidney: normal larger vessels, fibrous and hyaline thickening of the smaller arteries and arterioles and in

some areas a necrotizing arteriolitis. There were scattered focal hemorrhages in the pyramids. In sections stained for fat, essentially the same amount was found as in the first kidney examined, and with a similar distribution.

**Adrenals:** Beneath the capsule, in the

there was sclerosis. In the peri-adrenal tissue, some vessels showed lesions consisting of degeneration and hemorrhage into their walls; others contained fresh thrombi and still others were filled with organized and canalized thrombi (figure 17). There was an infiltration of lymphocytes, plasma cells,

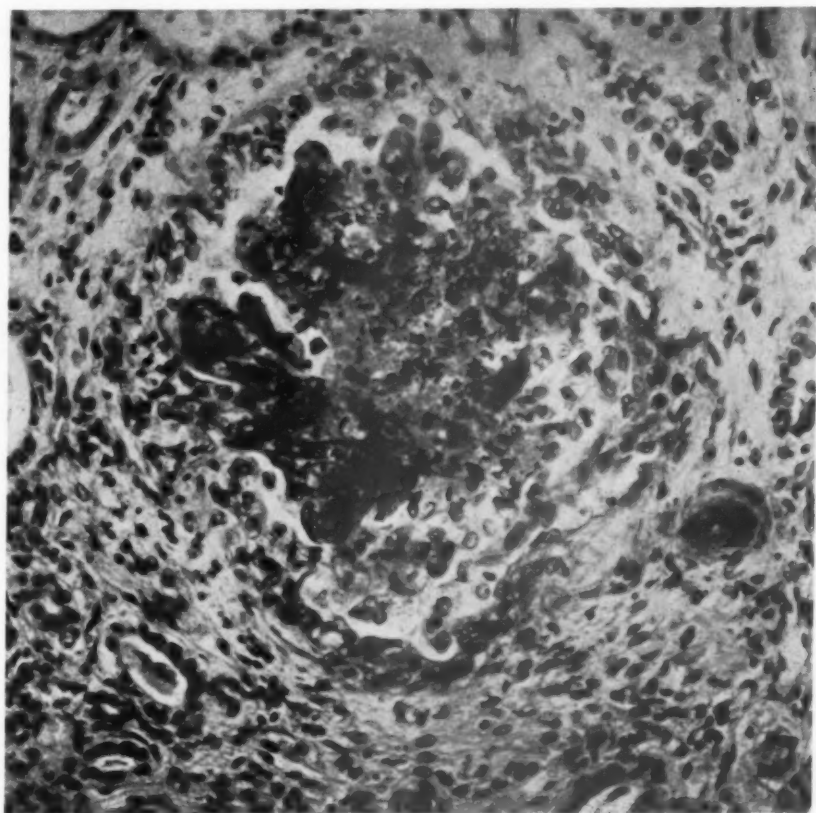


FIG. 11. Right kidney. Necrosis of glomerular tuft with hemorrhage. At the right can be seen a necrotic arteriole. X 275.

outer layers of the zona glomerulosa, there were numerous arterioles undergoing necrosis with fibrin formation in their walls. Other arterioles in this same region showed hyaline thickening of their walls. Adjacent to one necrotic arteriole (figure 16), there had been disappearance of the adrenal cells with an accumulation of large mononuclears containing fat. Scattered throughout the cortex were several focal collections of fat-laden macrophages and in one or two similar areas

and macrophages containing hemosiderin in the peri-adrenal connective tissue which appeared increased in amount. The walls of a number of thickened vessels contained a considerable amount of fat.

**Aorta:** There was a rare large mononuclear cell in the intima.

**Bone Marrow (Vertebral):** There was a normal number of cells of the erythrocytic, granulocytic and megakaryocytic series. A fair number of the last looked de-



FIG. 12. Right kidney. Necrosis of arteriole and glomerulus. X 500.

generated. Focal collections of stem cells were noticeable. Plasma cells were rather numerous. Only a few arterioles could be found and they appeared normal.

Bacteriology: Cultures of the heart's blood were negative.

*Quantitative and Comparative Histological Observations.* We had a unique opportunity

than in the right kidney at autopsy. While the majority of the cells in the right kidney were lymphocytes, there were also numerous polymorphonuclear neutrophils, especially in foci and in the lumens of the tubules. Indeed, the number of leukocytes, many of which were necrotic, in the tubules was so great that a pyelonephritis was suspected.

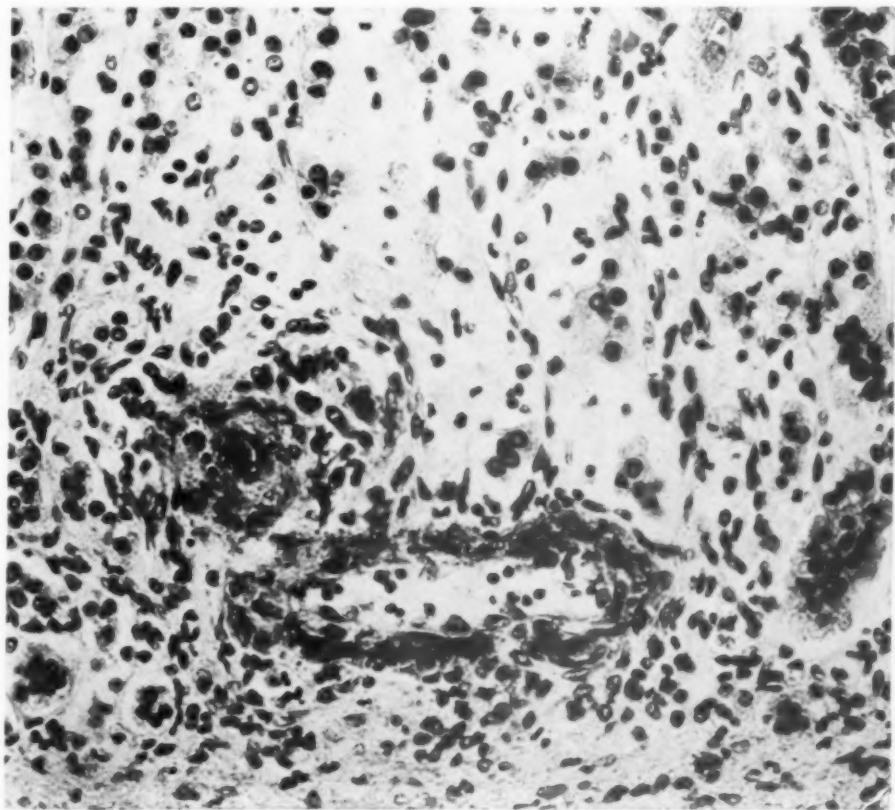


FIG. 16. Adrenal. Necrotic arteriole. Loss of parenchymatous cells below with infiltration of fat-laden macrophages. X 300.

to study the renal lesions at two different periods since one kidney was removed two months prior to the autopsy. In comparing the two kidneys, the most noticeable differences were found in the cellular infiltration of the stroma, the tubular changes, the glomerular lesions and the size of the kidneys.

The cellular infiltration in the left kidney removed surgically was much more marked

However, careful search of the sections failed to reveal any bacteria. Gross and histological study of the bladder and ureters also failed to reveal changes indicating infection.

The islands of dilated tubules found in the cortex of the autopsy specimen were noticeable and probably represented a compensatory dilatation. In this particular case there was great demand for compensatory func-

tion on the part of the remaining kidney since its load was suddenly doubled with the removal of the first kidney. The physiological studies described above demonstrate that it was able to carry on such a function during a comparatively short period.

In an effort to gain an idea of the relative

different types of lesions in the two kidneys. Obviously in both kidneys there were a number of normal glomeruli, but this number was considerably greater in the kidney removed surgically than in the kidney removed at the time of death two months later. The hypertensive type of glomerulus with thick-

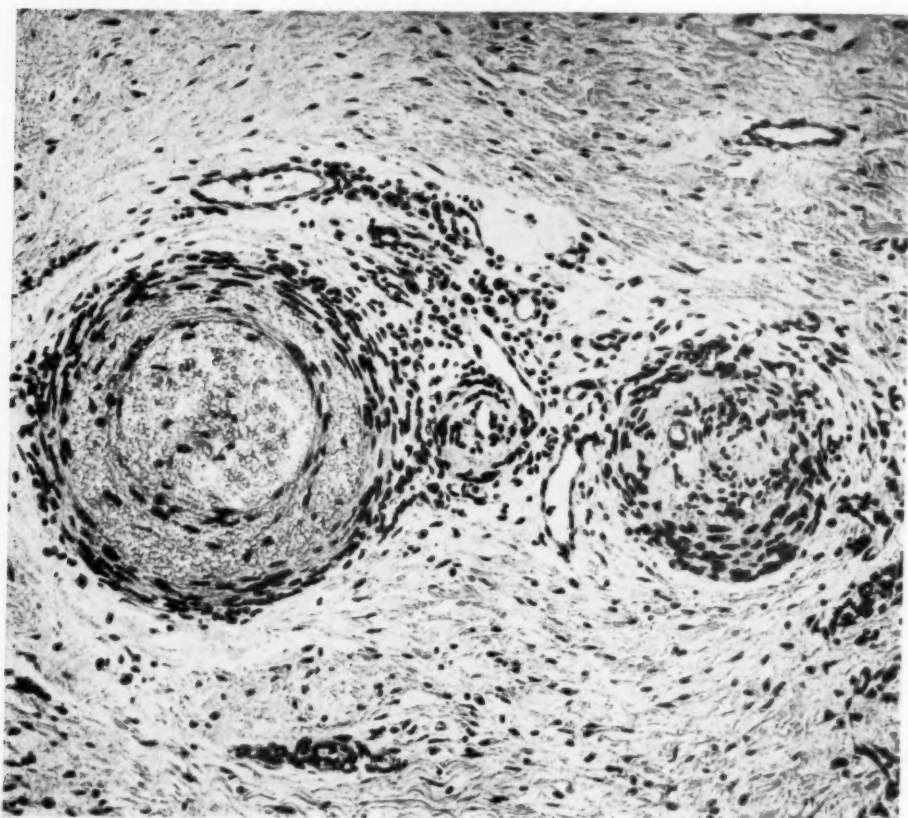


FIG. 17. Adrenal. Two arteries in periadrenal tissue. The one on the left shows hemorrhage into its wall, the one on the right contains an organized canalized thrombus. X 175.

frequency of the different types of glomerular lesions in the two kidneys, 300 glomeruli were studied in each kidney, after staining the sections with Mallory's anilin blue stain (Lee Brown modification). In this study several sections from different areas of each kidney were utilized. The results are given in table 6.

The data obtained by such a procedure serve to indicate the relative number of the

ened and wrinkled basement membrane was present in considerably larger numbers in the second kidney. Likewise hyaline, sclerotic glomeruli were more frequent in the autopsy specimen. It is of special significance that the type of glomerular lesion with an intracapillary meshwork of fibers and associated epithelial degeneration and proliferation was present in both kidneys but was somewhat less frequently found in the kidney

removed at autopsy. On the other hand, necrotizing arteriolitis and glomerular infarction were both much more prominent at the time of death.

The surgically removed (left) kidney weighed 213 gm. and was obviously considerably enlarged. The other kidney at the time of the patient's death weighed 165 gm. The size of the first was not due to operative clamping of the pedicle with resultant congestion since no evidence of this was found. It is interesting that the right kidney, in spite of its theoretical compensation, weighed almost 50 gm. less. There was no evidence

what appeared from the character of certain of the casts to be hemoglobinuria.

The acute disintegration of the glomeruli is considered a natural consequence of the thrombotic processes in vessels, with secondary acute or subacute ischemia. That under such circumstances leukocytic infiltration and other microscopic indications of an inflammatory process develop, is not unexpected. Such an abundant leukocytic infiltration was also noted by Shapiro.<sup>6</sup> One may compare this histological picture in the glomeruli with the changes in the myocardium following coronary thrombosis. Infection and, partic-

TABLE VI  
A COMPARISON OF THE GLOMERULAR LESIONS IN THE LEFT AND RIGHT KIDNEYS IN THE CASE OF MALIGNANT NEPHROSCLEROSIS

	N	H	I	S
	%	%	%	%
Left kidney, Nov. 18, 1930	27	28	32	13
Right kidney, Jan. 24, 1931	12	45	23	20

N = normal glomeruli,

H = hypertensive type of glomeruli,

I = glomeruli showing lesions of glomerulonephritis with or without an associated necrosis of the afferent arterioles,

S = sclerosed glomeruli.

that this kidney was congenitally hypoplastic; therefore, presumably its weight approximated that of its mate at the time of the nephrectomy. This decrease in weight might be accounted for by the diminution in the acute inflammatory exudate and by the loss of kidney parenchyma.

The vascular hemorrhages in this case were confined to the kidneys. It is possible that some may have occurred in the brain, but unfortunately permission to examine this organ could not be obtained. Histological examination revealed that the hemorrhages in the kidney were of three types—capillary, arteriolar and intratubular. The numerous capillary hemorrhages occurred in both kidneys and were almost entirely confined to the pyramids. The arteriolar hemorrhages, on the other hand, were found in the cortex. We attach special significance to the observation that hemorrhage into the tubules was common and marked in both kidneys, and in the second kidney was associated with

ularly, the presence of bacteria in such "inflammatory reactions" is not essential. A search for local infections in the kidney in this condition, therefore, may be futile, and perhaps the wrong approach to the problem.

It was stated above that there was evidence, as judged from the clinical course and laboratory tests, of an acute exacerbation with remission and a second flare-up of the acute process in the kidneys. Interestingly enough, this was confirmed by the histological findings. In addition, a similar picture was observed also in the lungs, liver, pancreas, and adrenals. The lungs showed an organizing process, as well as recent hemorrhages. The liver showed both a healed and an acute hemorrhagic central necrosis, thus pointing to at least two acute injuries, one some time prior to the other. In both the adrenals and the pancreas, areas of sclerosis as well as active focal lesions were present. In the peri-adrenal tissue there were several vessels containing organized and re-

canalized thrombi; in addition, in the adjacent connective tissue were numerous macrophages containing hemosiderin, evidently the remains of a hemorrhagic process. One vessel in the pancreas contained an organizing thrombus (figure 15), and its wall was degenerated and filled with nuclear debris. In brief, then, there were signs of healed

steady progressive nature of the disease. However, the sudden fluctuations in the clinical course suggest periodic healing and later exacerbation of the entire process in various organs with new and diffuse involvement of areas of minute vessels, rather than the progressive spread of the vascular disease into new areas.

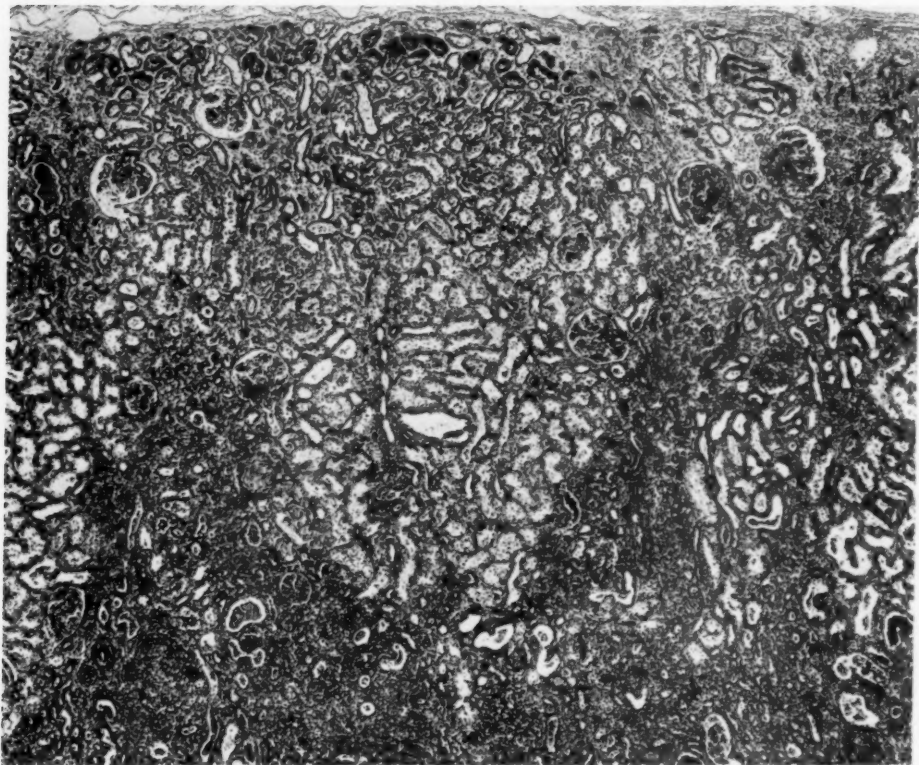


FIG. 5. Cortex of left kidney. Lack of dilated tubules. Infiltration of connective tissue with leukocytes. X 40.

lesions and acute lesions in various organs of the body indicating that there had been at least one acute attack in the past which had subsided and which was followed by another acute process found at the time of the patient's death. It is possible that with the progress of the disease more and more vascular units became involved. Thus, some minute vessels already showed chronic lesions at a time when others first became involved. Such an interpretation would indicate a

The changes noted in various organs illustrate once again that the lesions in malignant nephrosclerosis are by no means confined to the kidney but involve other organs as well. In our case, the vascular and parenchymatous involvement of the pancreas and adrenal was severe.

The acute and subacute changes in the bronchioles, atria and alveoli of the lungs with a normal state of the pulmonary blood vessels suggest that this pulmonary process



FIG. 6. Left kidney. Degeneration and proliferation of epithelium of glomerulus. One mitosis in lower lefthand corner. X 250.

was not related to the specific pathology of malignant hypertension. A bronchiolitis obliterans in chronic Bright's disease has been observed recently.<sup>32</sup> In view of the cardiac asthma and our interpretation of it, we are inclined to attribute the pulmonary changes to circulatory alterations resulting from relative and acute periodic failure of the left ventricle of the heart with secondary increased pulmonary pressure and transudations of plasma.

#### GENERAL DISCUSSION

The occurrence of an unusually rapid blood flow through the kidney in advanced malignant hypertension aids in the interpretation of the pathogenesis of the disease. This increased flow of blood existed, notwithstanding the fact that there was present partial and complete occlusion of nu-

merous afferent arterioles and capillaries of the glomeruli. It is probable that the increased blood flow through the kidneys was maintained by the elevated systemic arterial pressure. Although the earlier experimental obser-

In our case the high arterial oxygen saturation of the blood in the renal vein together with the ruptured capillaries in the kidney indicate also that the glomerular capillary pressure was increased. The presence of dilated

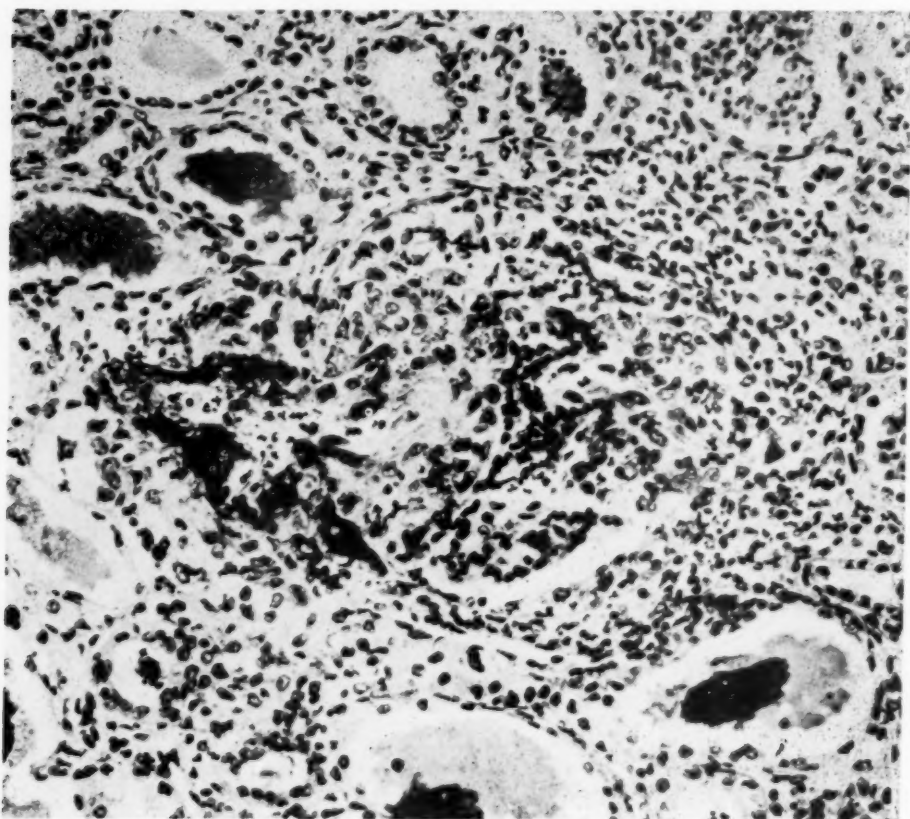


FIG. 7. Left kidney. Necrosis of arteriole and portion of glomerulus. Infiltration with polymorphonuclear neutrophils. Proliferation of glomerular epithelium. X 250.

ventions of Landergren and Tigerstedt<sup>33</sup> suggest that blood flow through the kidney has no relation to the level of the blood pressure, the more recent studies of Ozaki<sup>34</sup> and Moritomo,<sup>35</sup> with more reliable methods, reveal that a rise in arterial pressure increases the blood flow through the kidneys in animals.

afferent arterioles and capillaries of the glomeruli, an observation made also by Shapiro,<sup>6</sup> suggests an elevated pressure in the minute vessels of the glomeruli. Our finding of ruptured tubular capillaries suggests that the elevated pressure involved the tubular capillary system also, at least in a number of kidney units.

Although the histological structure and the exact distribution of the renal capillary system is not definitely established, a number of histological<sup>36,37,38,39</sup> and physiological studies<sup>40</sup> have furnished definite evidence that the emerg-

latory mechanism makes possible an increase of the capillary pressure in the glomerulus without necessitating a change in the pressure of the tubular capillary system. Such an independent change in the pressure relations be-

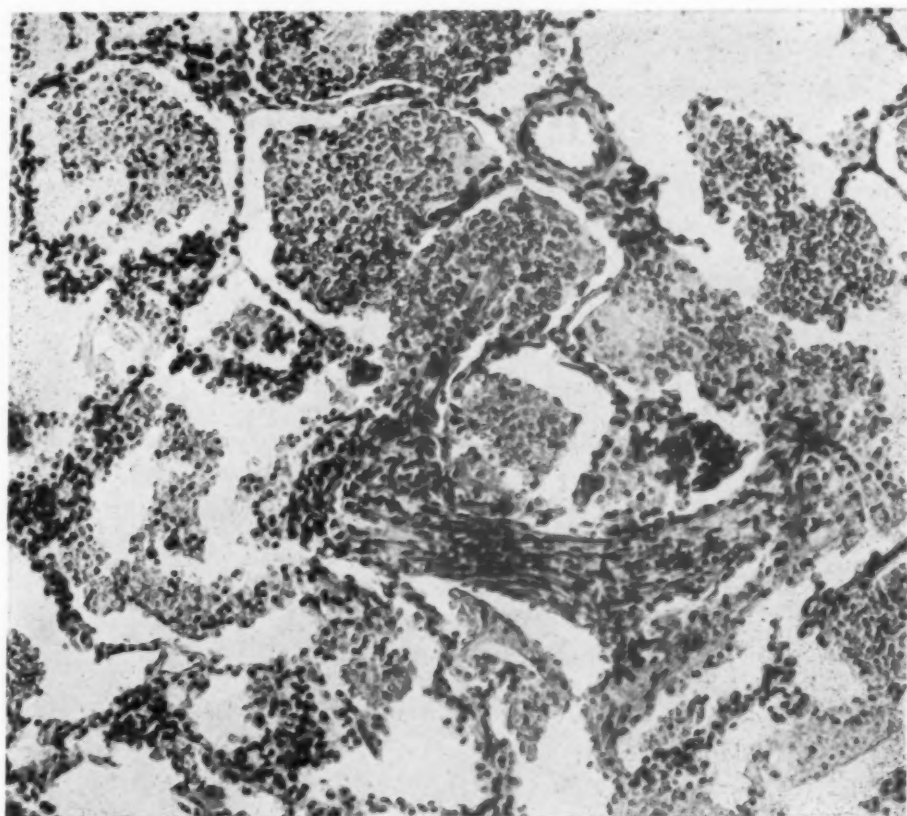


FIG. 14. Lung. One area of organized fibrin. Alveoli filled with red blood corpuscles. X 150.

ing portion of the efferent vessels of the glomeruli possesses special structures, which, probably through a sphincter-like function, allow the regulation of the blood flow through the physiological unit of the kidney. As the majority of the tubular capillaries are continuations of the glomerular capillaries,<sup>39</sup> the function of the regu-

tween the minute vessels of the glomeruli and tubules will result in better functional economy and increased filtration of urine without interference with reabsorption, so far as the latter can be influenced by hemodynamics. Depending on the degree of constriction of the efferent vessels of the glomeruli and on the simultaneous level of the

arterial blood pressure and on the size of the lumen of the afferent vessels, the glomerular capillary pressure may become elevated without a simultaneous increase or even with a decrease in the volume of blood flow through the kidney unit.

In the first place a number of the physiological units are completely eliminated. In a number of others there is a distinct structural change in the form of a thickening of the basement membrane. In these latter glomeruli, increased capillary pressure with nor-

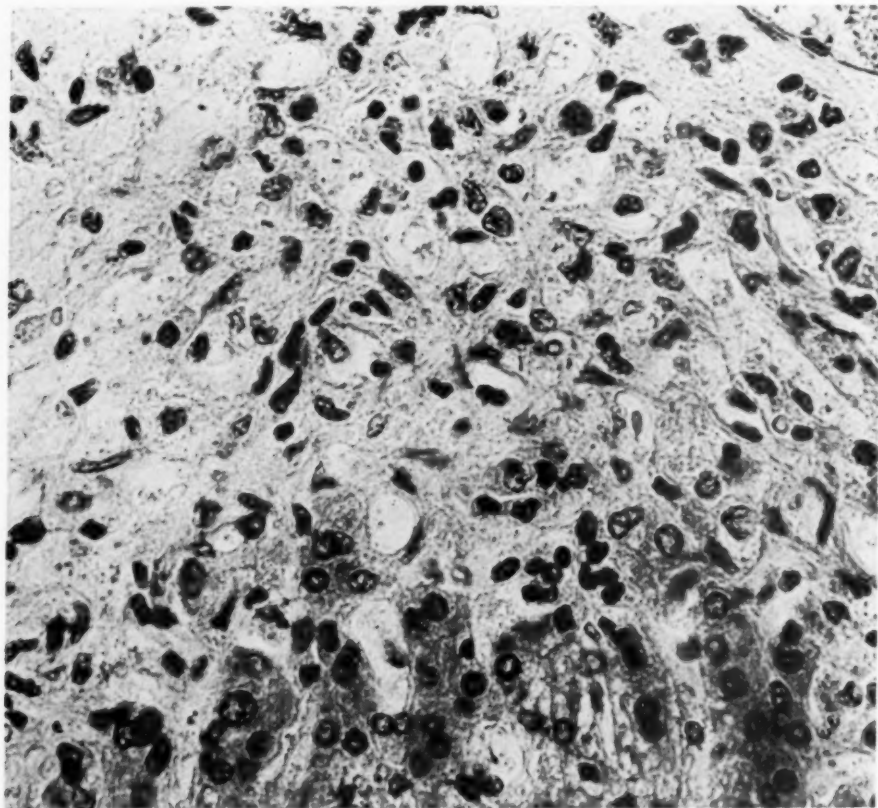


FIG. 18. Liver. Central sclerosis. X 250.

In this case of malignant nephrosclerosis, the increased blood flow together with the increased capillary pressure may be considered as a useful compensatory factor in the elimination of the waste products of the blood. In the light of the histological observations such an increased filtration pressure is beneficial for two reasons: (1)

mal or increased blood flow should improve filtration. (2) In the remaining number of normal glomeruli the circulatory changes, mainly through hypertension, induce an increased amount of filtration which compensates for the damaged glomeruli. Thus, the irregularly distributed morphological lesions of varying degree, that some-

what resemble focal glomerulonephritis, together with the observations on the functional state of the kidney suggest that in various units of the kidney the local hemodynamics as well as the secretory functions differ.

The increased volume of urine formation with fixed low specific gravity observed in the case is, therefore, not so much due to the impaired reabsorptive power of the tubules, as to the fact that in the 27 per cent of normal glomeruli, at the time the nephrectomy was performed, the volume and the velocity of the filtrate flow through the tubules was increased to a degree that prevented a correspondingly increased reabsorption by the tubules. The dilated and thin tubules in this and other cases are indications of increased filtrate flow under high intratubular pressure. In the physiological units with mild or severe lesions of the glomeruli the filtrate was probably less in volume and, therefore, as judged from the relatively normal histological appearance of the tubules, reabsorption may have occurred in a relatively more normal manner than filtration. The observation that the urea and creatinine clearance tests paralleled each other is also in harmony with this interpretation. The specific gravity, fixation of the urine volume per hour, and of the creatinine concentration index between blood and glomerular filtrate regardless of the water intake, also indicate that the kidney function was maximal in any given time. This, in view of the above findings on the hemodynamics of the kidney, is also to be expected.

Shapiro,<sup>6</sup> on the basis of his observations that in malignant nephrosclerosis the afferent arterioles and capillaries of the glomeruli were dilated, and that in-

jected India ink entered the wide afferent vessels of the glomeruli with ease, although the resistance of the kidney vessels was considerably increased, concluded that the pathogenesis of kidney changes depends "not on glomerular ischemia or on arteriolar occlusion, but on a hyperemia associated with a retardation of flow". This retardation is explained by him in accordance with Ricker's theory of a neurogenic dissociation in reaction between arterial constriction and peripheral dilatation. Shapiro does not offer any histological or other evidence, however, "for this neurogenic dissociation" nor for the existence of outstanding constriction of the larger or smaller arteries. His explanation would also fail to offer any rational explanation for the presence simultaneously of dilated and normal caliber individual glomerular capillary loops within the same glomerulus and hence supplied by the same small artery. The explanation offered by him would also necessitate the inference that the capillary pressure is decreased or at least not particularly increased in the glomeruli, a concept which is difficult to harmonize with frequent rupture of the kidney capillaries in this condition.

We realize that the evidence available from Shapiro's observations and the studies presented here do not permit at present the formation of a concept supported by sufficiently detailed direct observations; nevertheless, we favor the following working *hypothesis*, which in our opinion harmonizes all of the observations so far made.

The state of affairs in different units of the kidney in malignant nephrosclerosis at a given time differs considera-

bly. In the early stage of the disease a moderate constriction occurs in a certain number of efferent vessels of the glomeruli. These portions of the kidney capillary system have a rather specific structure, and the rôle of this vascular portion is similar in the kidney to that of the arterioles of other vascular areas. Their constricted state would correspond to the constricted arterioles in other organs observed in malignant hypertension. In accordance with the histological nature of malignant nephrosclerosis the degree of constriction is irregularly distributed. This focal scattered distribution of the histological lesions which was emphasized in this case has also been observed by us in a number of other cases. In the kidney units with severe vascular constriction which is out of proportion to the height of the arterial blood pressures relative stasis with increased pressure in the minute vessels, for reasons discussed above, will lead to dilatation of the vessels central to the emerging efferent portion of the glomerular vessel. It is this absolute or relative stasis with increased pressure in the glomerular vessels that leads to imbibition of metabolites by the adjacent structures, with resulting changes in the basement membrane as well as in the vessel wall itself. Simultaneously with these marked changes, in some of the glomeruli, with the progressively increasing arterial hypertension, the above described compensatory changes with rapid local blood flow and increased glomerular filtration occur. As the pathological process advances, involving larger numbers of vascular units, the number of normal units becomes so few that effective compensatory

elimination cannot be maintained and uremia ensues. Thus, near to the time of death there may be perhaps a decrease in the total blood flow through the kidney, while earlier the total blood flow, as was the case in this patient, is considerably increased. But even if the total blood flow is less than normal near to death, the volume flow through the remaining individual normal units must be increased considerably. This concept is in harmony with the general character of the circulation in arterial hypertension<sup>41</sup> and satisfactorily accounts for all the abnormalities detected in malignant hypertension.

It is obvious that the mechanisms of benign and malignant nephrosclerosis show a certain degree of similarity. There are, however, a number of differences in the clinical course and in the histology of the kidney in the two conditions. The youthful age of the patients, the fulminating fatal course, the markedly irregular distribution of the vascular lesions, and the character of the eyegrounds all suggest essential differences.

It is rather unfortunate that, because of the similarity in the mechanism of the two conditions, often no distinction in the etiology is made. The etiology of malignant hypertension is unknown. From the history and clinical study of a number of cases of malignant hypertension, we have been impressed with the frequency of severe infections. Tonsillar and peritonsillar abscesses, severe follicular tonsillitis, rheumatic fever, perinephritic abscess, pyelitis, and pyelonephritis were found in the cases observed by us in the past. Since it has been observed that the infection had often subsided at the time

when symptoms of malignant hypertension developed, one may justifiably assume that in malignant arterial hypertension an acute tissue response exists, which has a relation to infection, but which, if once precipitated, proceeds independently of infection. This indirect relationship between infection and malignant hypertension is apparently similar to the relation that exists between infection and certain allergic states.

#### SUMMARY

1. A study of malignant arterial hypertension with malignant nephrosclerosis is reported from observations on a case in which left nephrectomy was performed because of unilateral bleeding and suspected malignancy. The clinical course of the disease and the hemodynamics, function, and histological structures of the kidneys are analyzed and correlated.

2. Observations on the hemodynamics of the kidneys in three cases with normal kidney functions and cardiovascular systems, in which surgical suspension of the kidneys under spinal anesthesia was performed, served as controls.

3. The oxygen difference between the arterial blood and the blood from the renal vein in the three control subjects varied between 1.3 and 3.0 vol. per cent with an average of 2.4 vol. per cent. The average amount of oxygen taken from the blood by the kidney was 13 per cent of the average oxygen content of the arterial blood.

4. A comparison of the arteriovenous oxygen difference in the kidneys in these three subjects with that in the brain, heart, arm and leg indicates a

low oxygen difference and a relatively rapid blood flow through the kidneys.

5. No oxygen difference existed between the arterial blood and the blood from the renal vein of the patient with nephrosclerosis, which is interpreted as an indication of unusually rapid flow through the kidney.

6. The urea nitrogen changed from 13.0 mg. to 10.0 mg. per 100 c.c. in renal artery and vein in one of the control subjects and from 36.1 mg. to 32.5 mg. in the patient with nephrosclerosis. The urea and creatinine clearance performed during the surgical operation indicated adequate kidney function. The concentrations of creatinine and chlorides in the renal arterial and in the renal venous blood samples showed no demonstrable differences either in the control case or in the case with nephrosclerosis.

7. The nature of the functional disturbance of the right kidney after left nephrectomy was studied with repeated and simultaneously performed urea and creatinine clearance tests, and with the concentration and dilution tests.

8. The structures of the glomeruli of the left kidney were quantitatively compared with those of the right kidney; and it was demonstrated that within 67 days the number of glomeruli with thickened basement membrane and complete sclerosis increased considerably. The vascular sclerosis also became more extensive during this period.

9. Appearance of blood in the urine was caused by rupture of the minute blood vessels of the glomeruli and tubules as a result of increased pressure. The source of blood in the urine in ma-

lignant nephrosclerosis may be unilateral.

10. It has been demonstrated again that malignant hypertension is a diffuse disease of the vascular system with characteristic lesions in a number of organs.

11. The clinical course of the disease, the function of the kidney, and the histological analysis of the minute blood vessels of the kidneys and other

organs in this case of malignant hypertension indicated a tendency to fluctuate between improvement and relapses.

12. A concept is presented which correlates and interprets functional and structural changes observed in malignant nephrosclerosis with arterial hypertension.

We are indebted to Dr. F. B. Mallory for the photomicrographs used in this paper.

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## Changes Observed in the Heart Shadow in Toxic Goiter before and after Treatment\*†

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THE object of this study was to determine what changes take place in the size and shape of the heart before and after subtotal thyroidectomy for hyperthyroidism. One hundred and fifteen cases were observed in which roentgenograms were taken before and at various phases during and after treatment.

### CLINICAL MATERIAL:

#### ROENTGENOGRAPHIC METHOD

The group of patients studied in this report do not represent a consecutive series. Forty-six cases were followed from a consecutive series of one hundred<sup>1</sup>; the remainder were isolated cases which we have collected during the past five years. Roentgenograms were taken when the patient was first seen at the Clinic or within twenty-four hours after admission to the hospital. There were a few cases in which this was felt to be unwise owing to the patient's critical condition. The delay in such cases was rarely longer than two or three days. In seven cases, roentgenograms were taken again be-

fore operation and in the remainder, observations were made from one month to two years after operation, the majority within one year. Fluoroscopic observations were made in many of these patients, but orthodiographic tracings were not made.

Exposures were made with the subject standing at a seven-foot distance, during quiet breathing. The length of exposure time varied somewhat in the different hospitals but this could not account for the large differences in size found in some cases, nor for the changes found when all roentgenograms were made by the same person and with the same machine.

Measurements were made in the usual way and were then rechecked when all the films on each subject were available for comparison. This made possible a more uniform method of placing the points from which measurements were taken. When fluid was present in the chest, measurements were either impossible or less accurate than in the usual film. For this and other reasons, measurements alone cannot always be used to draw conclusions as to the change in the size of the heart shadow.

Comparisons of films were made in the following way: The contour of the

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heart, great vessels, diaphragm, and lateral chest wall were outlined (on all but nine films). The transverse processes at the root of the first rib and the first rib on the two films were superimposed and the lateral chest walls were made to coincide as nearly as possible. The outline of the heart on the underlying film could thus be seen plainly through the superimposed film, upon which it was then traced. Thus, on one film the outlines of both films were registered and the difference in the transverse diameter of the chest, the height of the diaphragm, and the changes in size and position of the heart could more clearly be seen and compared.

Even by this method of comparison and measurement, the statement that the heart shadow has changed in size is in many cases a statement of opinion and not of fact.

For instance, while a lower diaphragm and a relatively larger heart shadow in a follow-up plate mean an absolute increase in the size of the cardiac shadow, a lower diaphragm and a smaller heart shadow may or may not indicate a decrease in size. Thus all factors must be considered in each case.

#### AVERAGE HEART MEASUREMENTS BEFORE AND AFTER OPERATION

We obtained 46 roentgenograms after operation from a series of 100 consecutive cases of toxic goiter that had been roentgen-rayed before operation. The transverse diameters of the heart and the transverse diameters of the chest were averaged in these cases. In this group the transverse diameters of the heart after operation were larger

in 19 cases and smaller in 23 cases and the same in four cases.

The average transverse chest diameter before operation was 23.97 centimeters and after operation 24.56 centimeters. The transverse heart diameters averaged 13.07 centimeters before operation and 13.18 centimeters after operation. These averages would tend to indicate that the transverse diameters remain essentially unchanged and that the transverse diameters of the chest were increased by .6 centimeter. Such averages are misleading in considering individual cases, yet indicate the general trend that very little change takes place in the group as a whole. It would be possible, of course, for a true decrease in size of some cases to be offset by an apparent increase due to higher diaphragms in others, with a consequent maintenance of the same average transverse heart diameters for the group. Where this occurred the average transverse measurement of the heart would remain the same, though the average heart size was actually decreased. Our data could not safely be interpreted in this way.

From superimposed films it was concluded that the heart shadows of two of this series of 46 cases were larger, five questionably larger, and five smaller. Most of the cases with smaller shadows postoperatively in this series of 46 unselected patients had been admitted with congestive heart failure and auricular fibrillation.

A study of all the cases showing larger heart shadows after operation revealed that the majority had hypertension, coronary disease, rheumatic heart disease, persistent auricular fibrillation, or borderline myxedema. Large

gains in weight might reasonably be expected to be followed by larger heart shadows. Actually this was not conclusively demonstrated, although the evidence was quite suggestive in several cases.

#### INFLUENCE OF RHYTHM AND OF CONGESTIVE FAILURE IN CHANGES IN CARDIAC MEASUREMENTS

*Normal Heart Rhythm without Congestive Heart Failure.* Roentgenograms were taken on admission to the hospital and no sooner than two months later after operation in 80 cases of hyperthyroidism with normal rhythm. Twenty-three of these showed apparent changes in the heart shadow in the second plate as follows: In nine instances the heart was definitely larger and in six more questionably larger; in only six cases was the heart shadow definitely smaller; in two others the decrease in size was questionable.

*Normal Heart Rhythm with Congestive Heart Failure.* Seven cases showed congestive heart failure and normal rhythm. In one, the heart shadow was questionably larger when the patient was symptom-free, in two there was no definite change, and in four the heart shadows were probably smaller after clearance of heart failure. Three of these latter showed pleural fluid so that the measurements were only approximate, but comparison of the films showed obvious reduction in size. All of these cases showed coincident cardiovascular disease.

*Auricular Fibrillation without Congestive Heart Failure.* All of the observed patients who had auricular fibrillation without congestive heart failure on admission to the hospital, and

subsequently resumed normal rhythm, were operated upon before the normal rhythm returned. Consequently, we have no evidence as to the effect on the heart shadow when the transition from auricular fibrillation to normal rhythm occurs before relief of thyroid toxicity. We have taken roentgenograms before, during, and after postoperative auricular fibrillation. The results suggest an increase in size of the auricles from this irregularity alone. We observed an increase in size of the heart shadow following the onset of auricular fibrillation in a patient with exophthalmic goiter, mitral stenosis, and normal rhythm, who developed an attack of acute recurrent rheumatism a few days after hemithyroidectomy. Parkinson and Cookson<sup>2</sup> have recently described several cases showing an increase in the size of the heart shadow after the onset of auricular fibrillation.

Of eight cases in this series with auricular fibrillation uncomplicated by congestive heart failure, three showed postoperatively a definite reduction in the size of the heart shadow after normal rhythm was restored. Decrease in size was possibly present in the five others because of smaller transverse heart measurements, but the higher position of the diaphragms in these cases made the interpretation doubtful. Because there was so little difference in the superimposed films, the evidence did not appear sufficient to warrant a definite statement. One case with persistent auricular fibrillation appeared to show a larger shadow in the second film.

*Auricular Fibrillation with Congestive Heart Failure.* There were 16 cases with auricular fibrillation and conges-

tive heart failure and one with auricular flutter and congestive heart failure. Of these, 13 showed normal rhythm when the roentgen-rays

larger shadow. The latter case had hypertension and coronary disease and had had a mild recurrence of congestive heart failure although normal



FIG. 1 A. Heart shadow in a young woman, aged 31, with exophthalmic goiter, auricular fibrillation, and slight congestive heart failure. B.M.R. + 101, pulse 98, weight 108, blood pressure 160/90. Note prominence of pulmonary arc as well as region of left auricle.

were repeated. Of these 13 cases, nine showed definitely smaller heart shadows (see figure 1), two showed questionably smaller heart shadows, one showed no change, and one showed a

rhythm was present. The questionable cases probably were smaller as shown by the superimposed shadows, but the presence of fluid in the chest rendered the conclusions untrustworthy.

Four of the cases with auricular fibrillation and congestive heart failure did not have a return of normal rhythm after operation. Of these, two were

Thus it seems probable that auricular fibrillation is attended by some dilatation of the auricles and, in some instances, by dilatation of the ventri-

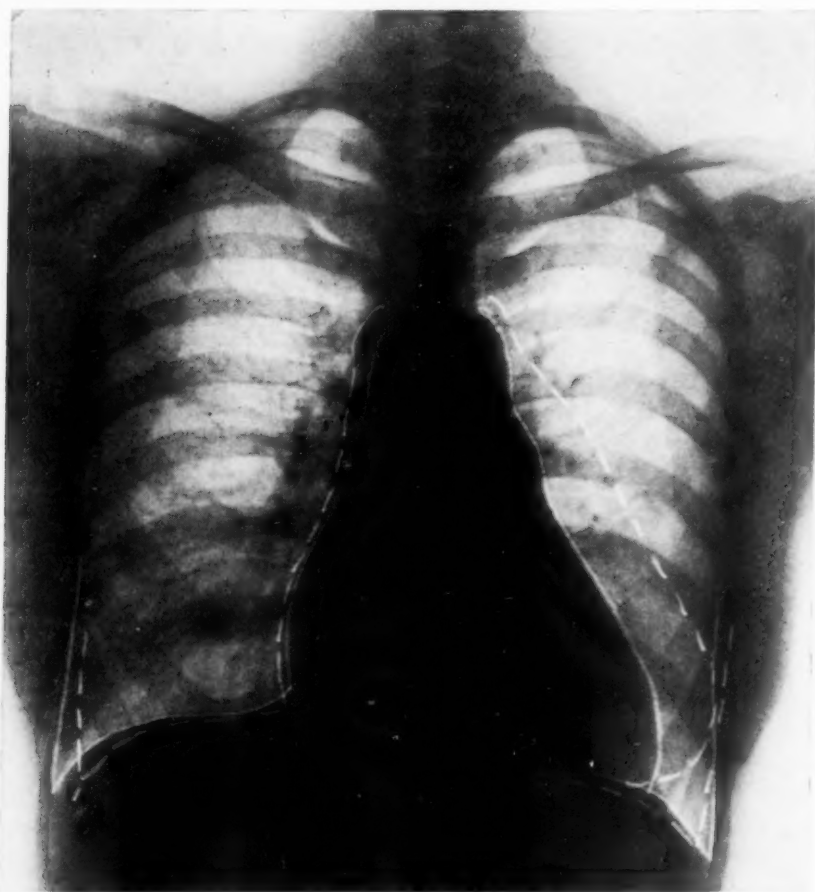


FIG. 1 B. Heart shadow 12 months later. Normal rhythm present. B.M.R. + 11, pulse 84, weight 120, blood pressure 140/90. Still slightly toxic and on Lugol's solution. The outlines of each film is superimposed upon the other. Note marked reduction along left side with diaphragms at same level. The prominence of the pulmonary arc persists.

questionably larger, one questionably smaller, and one definitely smaller.

In table 1 are shown the average measurements before and after treatment in this group of cases. It is to be noted that all measurements are smaller except the chest diameter.

cles. While we have made a sharp clinical distinction between patients with congestive heart failure and those without congestive heart failure, it is obvious, of course, that such a sharp differentiation cannot be made in all cases. Certainly, various degrees of

TABLE I  
AVERAGE MEASUREMENTS BEFORE AND AFTER TREATMENT IN 16 CASES WITH AURICULAR  
FIBRILLATION AND CONGESTIVE HEART FAILURE

	Average transverse diameter of chest in cms.	Average length in centi- meters	Average left border in centi- meters	Average right border in centi- meters	Average base in centi- meters	Average great vessels in centi- meters
Before treatment	23.8	16.1	10.6	5.1	10.6	8.1
After treatment	24.3	15.3	9.8	4.6	9.9	7.2

decompensation may be present before clinical signs of edema are manifest. When clear-cut congestive heart failure was present with auricular fibrillation, the heart shadow was larger than later when the fibrillating heart became well compensated. Further reduction seems to have taken place when normal rhythm was restored (figure 2).

#### CHANGES OBSERVED BEFORE OPERATION IN CASES WITH CONGESTIVE HEART FAILURE

Seven cases with congestive heart failure had roentgen-rays taken on admission and again after clearance of congestive heart failure. Five of these had auricular fibrillation and two had normal rhythm. Reduction in the size of the heart shadow in all cases was noted. In figure 2 is shown a case illustrating the successive changes in a patient with congestive failure and auricular fibrillation. Digitalis and Lugol's solution were given which, along with bed rest, cleared up congestive failure. (Normal rhythm was restored after operation and the heart shadow was further reduced in size.)

Congestive failure, in addition to auricular fibrillation, is undoubtedly partly responsible for the apparent

dilatation. Any treatment which clears up congestive heart failure, therefore, will probably produce a reduction in the size of the heart shadow. In some cases, Lugol's solution and bed rest will accomplish this result, but in others, in spite of this treatment, edema will increase, as we have frequently observed. Digitalis given at this point may produce marked diuresis. On the other hand, some cases with auricular fibrillation will show a reduction in ventricular rate following the use of digitalis but will not have diuresis until Lugol's solution is administered.

#### CHANGES IN THE SHAPE OF THE HEART

Attention has been called to the prominence of the pulmonary artery and other variations of the heart in toxic goiter.<sup>2,3,4,5</sup> More recently Parkinson and Cookson<sup>2</sup> described the heart in this condition as ham-shaped. They state that this type of cardiac contour is due to a combination of prominence of the pulmonary arc, the left ventricle, and, to a minor extent, the right auricle.

*The Pulmonary Arc.* In this series we found the pulmonary arc to be prominent (i.e., straight or convex) in 52 cases on first observation. In 19 of

these we felt there was a definite reduction in size of the arc after operation or after clearance of heart failure. Prominence of the pulmonary arc was observed in some patients without auricular fibrillation or congestive failure; but the reduction in its size was

most marked in patients with congestive heart failure.

*Transverse Diameter of Heart.* By measurement, the transverse diameter of the heart was increased after operation in 48 cases. The change in position of the diaphragm accounts for a

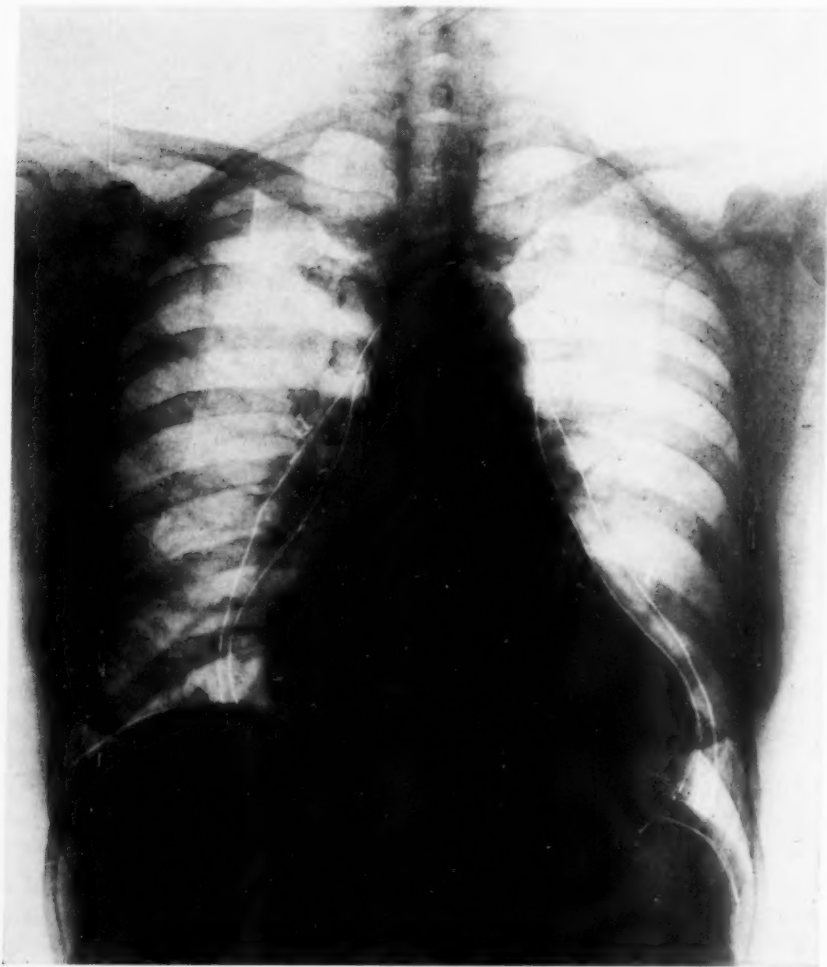


FIG. 2. Heart shadows in a woman, aged 38, with exophthalmic goiter of 24 months' duration. Auricular fibrillation, mild congestive heart failure (positive Wassermann). Outline (1) before treatment. B.M.R. + 69, pulse 104, weight 109. Outline (2) after digitalis and Lugol's solution. B.M.R. + 40, pulse 90, weight 102. Outline (3) 18 months later. Normal rhythm present. B.M. R. (?), pulse 88, weight 123. Note generalized reduction of heart shadow after clearance of congestive failure and then further reduction of right border after restoration of normal rhythm.

large number of these increases. The right and left borders participated in this increase, but the left border accounted for the greater part, being influenced more by the position of the diaphragm. Superimposed films revealed that the ventricles, as well as the auricles, took part in the apparent dilatation. When decrease in the transverse measurements took place, the left border receded more frequently than the right border, although the latter often showed relatively large recessions, particularly after disappearance of congestive heart failure and cessation of auricular fibrillation.

*Measurements of the Great Vessels and Base.* The position of the great vessels in the chest underwent little change except in some instances of congestive heart failure where they appeared to be pushed upward. The measured width of the great vessels, however, showed changes. Reduction in this measurement was frequently seen in failure cases and probably most commonly was due to a decrease in the size of the pulmonary arc, which is included in the measurement. In a few instances a decrease in the measurement to the right was noted, which was probably accounted for by displacement of the aorta. Displacement of the aortic knob to the left may be due to intrathoracic goiter. Removal of the goiter allows it to return to its normal position. Increase in measurements of the great vessels after operation were seen in a few cases where there was an increase in blood pressure.

The measurements of the base were usually reduced in the cases which had had congestive heart failure, although this was by no means constant. The

difficulty in making this measurement in some cases renders it, in our opinion, of little value for comparative studies. The length of the heart appeared to be greater in cases associated with hypertension or other heart disease. In some cases the length of the heart showed a distinct reduction in the second film, especially, as in the case of the other measurements, after congestive failure had subsided.

Thus all measurements of the heart seem to be affected by the altered shape of the heart in congestive heart failure.

*Other Changes Noted.* Prominence of the superior vena cava was very infrequently noted. In one or two cases with mitral stenosis, the shadow of the vena cava was easily distinguished. Increased hilus markings were noted in many cases but more commonly in the failure cases. Diminution in the intensity of these markings after relief of failure or after operation occurred frequently. In cases with congestive failure, as a rule, the diaphragms were elevated. At times this seemed to be offset by the usual drop of the diaphragm from loss of weight so that very little change in position was noted in successive films. The cause of this elevation has been ascribed to enlargement of the liver. However, pulmonary congestion tends to render the lung tissue less elastic by virtue of the engorgement of the alveolar capillaries. In this way diminished vital capacity is brought about. Secondary atelectasis may occur. Thus it is reasonable to assume that the higher position of the diaphragm can be accounted for by these factors as well as by liver engorgement.

## DISCUSSIONS OF FACTORS INFLUENCING THE SHAPE OF THE HEART IN HYPERTHYROIDISM

The cause of the prominence of the pulmonary artery in toxic goiter is unknown. There seems to be little doubt that it occurs, though the frequency of a straight or convex arc is rather high in patients without hyperthyroidism. In a consecutive series of teleoroentgenograms on 100 toxic goiter cases, 100 non-toxic goiter cases, and 100 non-goitrous individuals of approximately the same age and sex distribution, we found a straight or convex pulmonary artery region in 43, 30, and 32 per cent respectively. The most prominent arcs, however, appeared in the toxic goiter cases. Postmortem measurements made by Parkinson and Cookson<sup>2</sup> in six cases showed a 17 per cent increase in circumference of the pulmonary artery compared to normal standards. This should be confirmed by a larger series. This prominence must therefore be due to dilatation of the pulmonary artery presumably from increased pressure in this vessel.

Since enlargement of the pulmonary arc occurs without evidence of congestive heart failure, the origin of the increased pressure must be between the right ventricle and the pulmonary arterioles. Hyperthyroidism is characterized by a decreased peripheral arteriolar resistance but whether this drop also occurs in the pulmonary circuit is unknown. A vasomotor mechanism in the smaller vessels of the lung probably exists,<sup>6</sup> but it is doubtful if the vascular bed in the pulmonary circuit would permit of vaso-dilatation to such a magnitude as occurs peripherally. If this assumption

is true, then, with the increased output of the heart, the right ventricle would be working against a constant pressure in the pulmonary circuit. This inequality in pressures might soon lead to a gradually increasing intra-pulmonary arterial pressure and eventually dilatation of the pulmonary artery itself. In other types of heart disease increase in pulmonary pressure probably has its origin in the left ventricle and is transmitted backward to the pulmonary circuit or, as in mitral stenosis, it still begins in the left side of the heart but at the mitral valve. Thus in one, pulmonary pressure is elevated first at the pulmonary arterioles and transmitted back to the right side of the heart, and in the other the pressure begins at the arterioles of the systemic circulation, in the left heart or at the mitral valve and is transmitted back through the pulmonary veins to the pulmonary capillaries. Increase in pulmonary vein pressure may give rise to hemoptysis, paroxysmal dyspnea, and marked orthopnea. Increase in pulmonary artery pressure, as long as secondary effects do not take place, should not give rise to these manifestations. This seems to be borne out by clinical experience. Gallop rhythm is frequently seen in very toxic patients with hyperthyroidism and regular rhythm. Perhaps here too the relative inequality of pressure might play a part.

That the right ventricle becomes hypertrophied as well as the left is shown by postmortem examinations.<sup>2</sup> When gross left ventricular hypertrophy is seen in roentgenograms as indicated particularly by the blunt appearance of the ventricular shadow, hypertension is usually present and the

pulmonary arc is often less conspicuous. Enlarged auricular shadows contribute to the configuration of the heart in toxic goiter, the right probably more often than the left. When auricular fibrillation and congestive heart failure are present, dilatation of the auricles substantially alters the shape of the heart.

The incidence of the so-called ham-shaped heart is not great in our series. There are several explanations for this: First, surgical treatment is in more favor in this country than elsewhere, consequently, cases are referred for surgical treatment early in the course of the disease. Second, hyperthyroidism is generally more easily recognized than formerly, with the result that a larger number of patients over fifty, in whom hyperthyroidism is more difficult to diagnose than in those of younger years, are detected. Naturally, the incidence of other cardiovascular disease is high in these cases, the presence of which influences the shape of the heart.

#### SUMMARY\*

Roentgenograms were made before and after treatment in 115 cases of

\**Editor's note:* An extensive tabular report of cases is not published because of limitation of space.

toxic goiter. Comparisons of films were made by measurement and by superimposition. *Definite reduction in size* was observed after relief of congestive heart failure, and after cessation of auricular fibrillation, and in a few without these complications. Factors contributing to the shape of the heart in toxic goiter are enumerated and their probable causation discussed.

#### CONCLUSIONS

1. Superimposition of seven-foot roentgenograms of the heart is the most satisfactory method of judging changes in the size and shape of the heart.

2. Very little change takes place in the heart shadow in uncomplicated cases of toxic goiter with normal rhythm following removal of thyroid toxicity by subtotal thyroidectomy.

3. Cardiac dilatation as shown by roentgenograms takes place most frequently in congestive heart failure with or without auricular fibrillation.

4. Occasionally in cases of toxic goiter of sufficient duration, uncomplicated by other cardiovascular disease, certain changes in the heart shadow may be found which have been described as characteristic of hyperthyroidism.

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## Discussion of a Case of Gastric Carcinoma with Recurrent Colic\*†

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NO reference is made in the literature to carcinoma of the stomach, producing attacks of pain resembling gall-stone colic. I wish to present such a case. The patient had attacks of typical gall-stone colic: sudden, severe pain in the right upper part of the abdomen under the costal margin, always requiring opiates for relief, and radiating always to the right shoulder region. Associated with this pain there were varying degrees of shock, manifested by pallor, rapid pulse, perspiration, weakness and prostration.

Pain is one of the common symptoms in cancer of the stomach. It varies considerably in its intensity, though the degree of distress is usually not excessive. In the early stages the patient may complain only of a sense of discomfort after meals, but as the condition progresses, actual pain manifests itself. There is nothing characteristic about the pain. It is usually of a dull, gnawing type; in some, it is of a burning character, and in others it may be sharp and lancinating. Cramp-like pains occur when there is associated pyloric

stenosis. In a few cases it may be so constant and severe as to be almost unbearable. Exceptionally, gastric carcinoma may occur with little or no pain. The pain may be intermittent or continuous. When intermittent it may occur only every few days or weeks. In not a few cases it is only nocturnal in its appearance.

A relation to food may or may not exist. Often foods increase the pain, especially if the cancer be pyloric, and in such instances, as in ulcer, it is usually relieved by vomiting. Or the pain may be continuous and bear no relation to the ingestion of food.

The site of the pain is usually in the epigastrium. It may, however, be complained of at the following sites: in the right upper quadrant, in the interscapular region, at the lower end of the sternum, low in the abdomen and at times in the left hypochondrium.

### CASE HISTORY

S. P., age 58, peddler by occupation, reported to the Gastro-Enterologic Clinic at the Temple University Hospital on August 12, 1931. His past medical history was negative except for an attack of lobar pneumonia in 1917 and a double herniorrhaphy and appendectomy in 1919. He was perfectly well until one year ago when he had a nocturnal attack of sharp pain in the right upper quadrant, under the costal margin, which radiated to the back and the right shoulder area, and

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also across the abdomen to the left. The pain was of such intensity that a physician had to be called, and it was relieved only by the administration of a hypodermic of morphine. Since then he has had recurring attacks of similar pain, generally a few weeks apart, mostly diurnal and in each attack the pain was so intense that no relief was obtained until morphine was administered subcutaneously. There was no jaundice, chills or fever associated with the attacks, nor any urinary phenomena. The pain appeared without relation to food ingestion, or to physical exertion. His only worries were as to his health; he had no sorrows or griefs. There was no premonitory warning of an impending attack. An attack was never followed by any gastric disturbances such as nausea, vomiting or belching.

There was a loss of six pounds in weight in the past six months, and there was considerable loss in strength, so that for the last two months he felt he did not have sufficient stamina to carry on his work. His appetite lately was poor. There were no postprandial discomforts. The stools were light yellow to light brown in color and frequently contained mucus. There was never any blood in the stools.

**Physical Examination.** An adult Jew, of hyposthenic build, who appears to be about 60 years old. He is in no discomfort at the time of examination. Weight 125 pounds; height five feet, five inches. The pupils are equal and react normally to light and accommodation. The skin of the face is dry, weatherbeaten, and somewhat wrinkled. The tongue is clean, the teeth worn down and discolored, and the gums show food deposits. The tonsils are cryptic, the pharynx is congested, and there is a moderate cervical adenopathy. The thyroid is not palpable. The lungs are grossly negative; respiratory rate twenty. The heart is normal in size; the heart sounds weak; no murmurs present. The palpable arteries are slightly sclerotic. Blood pressure 140 millimeters of mercury systolic and 80 diastolic. Pulse rate 84.

The abdomen is scaphoid. There are two inguinal scars of a former herniorrhaphy. There is a tenderness in the epigastrium and over the gall-bladder region. There is no increased muscular tension anywhere nor is

any mass palpable. The liver edge is felt one centimeter below the costal margin. The spleen and kidneys are not palpable. The sigmoid is spastic. The rectal examination is negative except for external hemorrhoids. The knee jerks respond normally. Romberg test normal. Coördination normal. Babinski test negative.

The tentative diagnosis was cholelithiasis.

The routine studies made were as follows:—

**Gastric.** Fractional gastric analysis yielded a pearly-grey fasting residuum of ten cubic centimeters. There was no gross food retention, blood or pus present. Microscopically no Boas-Oppler bacilli or yeast cells were found, and there was no microscopic evidence of food retention.

The acid determination, employing an Ewald meal stimulus and one-half hourly extractions, was as follows:

	F	1	2	3	4
Free	0	0	22	22	32
Total	28	36	54	54	50
Bile	Pos.	Pos.	Pos.	Pos.	Pos.
Occult	Pos.	Pos.	Pos.	Pos.	Pos.
Blood	#1	#1	#1	#1	#1

As is seen, bile was present in the fasting and digesting stomach. The patient had taken the tube without gagging. According to Lyon<sup>1</sup> this is an abnormal finding and points either to disturbed physiology of, or to pathologic lesions within, the pyloro-duodeno-biliary apparatus. There are two exceptions to this: first, if the patient does not take the tube well but gags and coughs, bile may be regurgitated into the stomach; second, in cases of marked hyperacidity, the alkaline duodenal contents mixed with bile may be regurgitated into the stomach in a physiologic effort to lower the excessive acid. This latter mechanism is questioned by some observers.

We often find it difficult properly to evaluate the presence of occult blood. It is an abnormal finding if good tube technic is carried out. In office practice

where our technicians are properly trained and there is no hurry, the presence of occult blood is of considerable significance, and implies to us that we are dealing either with congestion, or erosion, or ulceration of the mucous membrane. But in clinic work, because of the large number of patients and the need for attention to as many as possible, tube technic is unfortunately not carried out with the same necessary care. We frequently find our technicians employing unnecessarily strong syringe suction in an attempt to extract a fraction hurriedly. Unless the benzidine reaction be very strong and the guaiac test positive, we attach no importance to occult blood reactions in the clinic. We grade our occult blood reactions plus one, two, three, and four. In plus one reactions we always think of trauma. In addition to trauma as a factor, we must also rule out mouth suction on the part of the patient. A good plan is to have the patient produce suction on his gums and then expectorate the material into a clean dish and test it for occult blood. The latter may also occur as a result of cricopharyngeus muscle spasm in the vagotonic type of individual. Physiologically, the two points of tonus in the esophagus, according to Jackson, are at the crico-pharyngeal orifice and at the hiatus. Vagotonics with excessive muscle strain can, during gagging, readily produce trauma at this upper point, and they often complain that they are sore, pointing over the cricoid cartilage, for some period of time after having had intubation of the stomach or duodenum. Even when the occult blood reaction is marked we must still keep in mind the possibility that we

may be dealing with a friable gastric mucous membrane. There is also the possibility that the presence of occult blood in any one fraction of the digesting stomach may be due to an abnormal amount of peristaltic contraction against the tip of the tube with consequent mucous membrane erosion.

We do not examine the gastric contents routinely for lactic acid because it is our opinion that it is not diagnostic of carcinoma. We do not agree with MacLean<sup>2</sup> who emphasizes the great value of its presence and who claims that it occurs frequently in large amounts at a very early stage in carcinoma. It is our conviction that lactic acid indicates only that stagnation has occurred and that gastric acidity is disappearing, and that it may accordingly be present not only in certain forms of gastric carcinoma but also in the benign pyloric stenoses when these cause a marked degree of obstruction, and may indeed be found in cases of marked motor insufficiency. This agrees with the findings of Murray and Robertson<sup>3</sup> who reported that an investigation of test meals from 50 subjects, pathologic and normal, showed the presence of lactic acid in 74 per cent; it occurred more frequently in hyposecretion but was found present even in hypersecretion. Their conclusion was that lactic acid had no apparent clinical significance.

The Ewald meal was completely evacuated at about the two hour point, which indicates that gastric motility was normal. The final lavage revealed no food sediment remaining.

*Biliary.* A number of biliary drainages failed to show any cholesterol crystals or calcium bilirubinate pigment to be present.

The B fractions were of normal brown

color, and microscopy of all fractions failed to show evidence of any inflammatory involvement of the biliary system.

Bockus et al<sup>4</sup> have demonstrated that the finding of cholesterol crystals or calcium bilirubinate in the same bile is pathognomonic of gall-stones; and that the diagnoses of gall-stones based on the finding of cholesterol crystals without the characteristic pigment are 89 per cent accurate, and those based on bilirubin calcium pigment are 90 per cent accurate. It has been our experience that if in a number of successful drainages, i.e., those yielding good B fractions, we have failed to recover one of these two elements, especially in a centrifugated specimen, we may feel safe in saying that stone, in all probability, does not exist in the gall tract.

*Urinalysis.* Negative, except for trace of albumin. No pus cells or red blood cells were noted on a number of examinations.

*Stool Study.* The stools were of average size, light yellow in color, and of the usual fecal odor. There was no blood, gross or occult; no mucus, pus, nor grossly recognizable undigested food elements were present. Microscopy showed no free fat or undigested muscle fibers, indicating no failure of the external pancreatic or intestinal functions.

*Blood Count.* Hemoglobin, 85 per cent; red blood cells, 4,350,000; white blood cells, 7950. Differential white count, normal.

*Van den Bergh Reaction.* Direct, negative; Indirect, 0.2 unit.

*Icterus Index.* Six.

*Liver Function Studies.* Bromsulphalein: 2 milligram dose showed no retention at the end of 30 minutes. Galactose Tolerance, 3.3 grams. Urobilinogen, 1:5; Wallace and Diamond method, in which readings up to 1:10 are considered normal.

*Blood Chemistry.* Urea N 12 milligrams per 100 cubic centimeters; sugar 120 milligrams per 100 cubic centimeters.

*Wassermann.* Blood Wassermann and Kahn tests, negative. Spinal fluid Wassermann negative.

*Blood Sedimentation.* Normal horizontal line (Cutler graph).

The blood sedimentation test<sup>5</sup> is a laboratory procedure which seems to have found a place as a valuable aid in diagnosis. When positive, it is an early indication of the presence of a destructive process as well as a measure of the intensity of the disturbance. Essentially the sedimentation phenomenon depends upon the amount of cellular destruction going on in the body. In healthy persons, as a result of the wear and tear of everyday life, a certain amount of tissue destruction is always taking place, and although this varies daily it remains within limits considered normal. Should, however, the amount of tissue destruction pass beyond the normal, then the stability of the blood is seriously disturbed and the red blood cells settle out quickly from the plasma. The rapidity of the settling of the red blood cells is in direct proportion to the severity of the underlying destructive process.

*Roentgenologic Study (Dr. Chamberlain).* No abnormality of the esophagus. The stomach is of average normal size, shape and position. Its outlines are smooth and regular throughout and its walls normally flexible. Gastric peristalsis begins soon after taking the barium meal and the stomach starts to empty in the normal manner. The outlines of the pylorus and the duodenum are likewise normal, but there is persistent tenderness in the right upper quadrant of the abdomen.

At six hours the stomach is empty and the barium is divided between the pelvic ileum and the cecum. The cecum is freely movable and not tender.

At 24 hours the distribution of the barium in the colon is normal and no abnormality of the large bowel is noted.

Films of the gall-bladder region, 13 hours after four grams of tetradol emulsion by

mouth, showed only a very faint gall-bladder shadow. To check up on this finding, the procedure was repeated on the following day. With the second examination we obtained 13 hour films which showed a gall-bladder of normal size and density, at the level of the disc between the second and third vertebrae. Films made two hours after a high fat meal showed the gall-bladder much smaller.

*Conclusions.* We have discovered no roentgen-ray evidence of organic disease in the gastrointestinal tract, and the findings in the gall-bladder suggest normal function.

*Gruskin Test for Malignancy.*<sup>6</sup> Positive for carcinoma.

The Gruskin test is a flocculation reaction based upon the theory that, under normal conditions, epithelial and connective-tissue cells produce lysins that are antagonistic to each other and that due to their presence an equilibrium between these two types of cells is maintained. Because connective-tissue cells generate lysins which prevent the overgrowth of epithelial cells, carcinoma does not develop even though inciting factors (irritation, etc.) may be present. If, however, the connective-tissue fails to generate such lysins and the proper extrinsic factors are present, then carcinoma develops. The opposite condition holds true in the production of a sarcoma. That normal serum has the ability to autolyze cancer cells in vitro, whereas cancer serum fails to do so, has been demonstrated by Freund and Kaminer.<sup>7</sup> In other words, in malignancy there is present in the blood stream a protein which is characteristic of the type of tumor, carcinoma or sarcoma, from which the patient is suffering, and this protein is typical for the type of embryonic cells of which the tumor mass is composed. When the serum of a patient suffering

with malignancy is brought in contact with an extract of embryonic cells of a homologous nature, flocculation takes place; when serum of a normal individual is thus tested, no such flocculation occurs.

Because of the positive Gruskin test and the normal sedimentation, we had to assume that malignancy, if present, was still in an early stage, that is, before tissue destruction had begun. A normal sedimentation rate is not conclusive evidence that there is no tissue destruction but it does show that disease, if present, is producing very little, if any, constitutional disturbance.

Because of the absence of positive findings, i.e., normal B fractions, negative bile microscopy and negative cholecystography, it was obvious, in spite of the fact that the symptoms were characteristic, that the diagnosis of cholelithiasis was probably not correct. There are a number of conditions that may produce attacks of pain resembling gall-stone colic. We therefore had to consider one of the following as a possible cause: cholecystitis; carcinoma of the gall-bladder; peptic ulcer, especially the perforating type; gastric crises of tabes; renal colic; appendicitis; pancreatitis; pancreatic calculus; lead colic; angina pectoris, and floating kidney. Weir and Partch have called attention to the fact that colicky attacks resembling gall-stone colic may also occur with cholangitis, cirrhosis and hepatitis, stricture of the common bile duct, and carcinoma of the pancreas.

*Cholecystitis.* Attacks of pain indistinguishable from gall-stone colic may occur in cholecystitis. The diagnosis is based on positive microscopic findings

of the biliary aspirates. The examination will reveal bile-stained, exfoliated, tall columnar epithelium often arranged in fan-shaped groups or rosettes; an excessive amount of mucus which may be encrusted with bile salts; an increased number of leukocytes proportionate to the extent of the inflammatory process; amorphous debris and occasional red blood cells. It must be remembered that negative findings do not necessarily indicate that there is no pathologic lesion, and in clinically suggestive cases if microscopy in the first study is negative the examination should be repeated.

Because of the absence of fever and leukocytosis, as well as the absence of positive microscopy over a number of drainages, and the presence of good function as demonstrated by cholecystography, the diagnosis of cholecystitis could not be supported.

*Carcinoma of the Gall-Bladder.* In the early stages, cancer of the gall-bladder often resembles cholelithiasis. In about 80 per cent of the cases gall-stones are found, and it is held by many that calculi are responsible for this condition. Because of the positive Gruskin test, this was a diagnostic possibility.

*Peptic Ulcer.* Gastric or duodenal ulcer, especially those with a tendency to perforation, may give rise to attacks of pain resembling gall-stone colic. Even with modern methods of study, mistakes in diagnosis between these two conditions are frequently made. As a rule the pain of ulcer has a direct relationship to food but so has the pain in certain cases of cholelithiasis, and in the latter the pain may be aggravated in some instances by dietary in-

discretions just as in ulcer. The pain of cholelithiasis in some cases may be present after every meal, and in cases of peptic ulcer there are usually well marked periods in which the patient is nearly or quite well. Hyperacidity speaks for ulcer, but according to Moynihan's statistics 22 per cent of his cholelithiasis cases showed hyperacidity, and in Rehfuess' experience more than one-half of his cases show hypersecretory findings. Though hematemesis and melena may occur in cholelithiasis it is an infrequent finding, whereas the presence of these symptoms speaks strongly in favor of ulcer.

The absence of such symptomatology in this case and the negative roentgen picture were against this as a diagnosis, although negative roentgen-ray findings do not exclude ulcer.

*Gastric Crises of Tabes.* The normal reflexes and the negative blood and spinal fluid Wassermann reactions excluded this condition as a possibility.

*Renal Colic.* The colic of nephrolithiasis is, as a rule, easily distinguished because of the radiation of the pain to the groin, the frequent micturition and the presence of blood, pus or albumin in the urine.

No stones were seen on flat plates. Urine examinations were persistently negative.

*Appendicitis.* Occasionally the cecum may be undescended, in which case the appendix lies close to the gall-bladder and an acute attack will be productive of pain simulating gall-stone colic.

The past history of appendectomy excluded this.

*Pancreatitis.* The pain in this condition is more directly in the epigastrium or to the left; there is a deep-seated

tenderness and resistance over the pancreatic area, and in an acute attack the shock and collapse is great and early in onset. Chronic pancreatitis may sometimes be detected by stool study; the movements are usually large, soft and pultaceous, and there is present free fat and undigested muscle fibers.

Normal stool findings over a number of studies, as well as the absence of such symptoms and physical findings as noted above, were against this condition being present.

*Pancreatic Calculus.* Colic may occur as the result of the passage of a calculus along one of the ducts of the gland. There is severe, deep-seated epigastric pain, generally associated with vomiting, glycosuria, steatorrhea and azotorrhea. The condition is rare and is usually mistaken for gall-stones.

The absence of the associated symptoms and signs did not favor such a diagnosis.

*Lead Colic.* Lead, by its stimulation of the motor nerves in the intestinal wall, causes violent spasm and contraction. The pain is felt about the umbilicus but often radiates from there into the right hypochondrium, suggesting biliary colic. The presence of anemia, a blue line in the gums, obstructive constipation, stippling of the red blood cells, tremor, palsies and an occupation involving exposure to lead suffice to make a clinical diagnosis.

The absence of the above symptoms exclude this from consideration.

*Angina Pectoris.* The pain of angina pectoris not infrequently may be referred to the epigastrium or to the right upper quadrant of the abdomen and may simulate an acute surgical abdomen. In such cases an acute coro-

nary occlusion is often the cause. In Heberden's angina pectoris the pain occurs or follows immediately upon effort; an attack may be induced by emotion and excitement, may follow upon exposure to cold, or may occur with gaseous distention after a heavy meal.

The patient was studied by the Cardiac Department and no cardiovascular lesion was found to be present. The electrocardiogram revealed no evidence of coronary disease.

*Floating Kidney.* That undue renal mobility, by producing traction on the duodenum and common bile duct or by kinking of the cystic duct, may induce attacks of biliary colic, has been pointed out by a number of observers. Marwedel<sup>8</sup> states "a movable right kidney may produce all the symptoms of cholelithiasis—colic with or without jaundice—in the absence of diseases of the biliary passages". Moynihan<sup>9</sup> refers to movable kidney as having caused confusion in diagnosis in some instances. Sherren<sup>10</sup> has discussed this subject fully. He states "among thirteen cases in which symptoms suggestive of cholelithiasis were associated with movable kidney all except one were women. Gall-stones were present in two cases only. In none had urinary symptoms occurred. With regard to differential diagnosis this is difficult; even when the symptoms are due to movable kidney alone, tenderness will be present in the gall-bladder region during the attack, and Murphy's sign may be marked. When jaundice exists, the fact that the gall-bladder is distended should make us suspect that the movable kidney is the cause."

The attacks are almost always diurnal.

nal. The diagnosis depends on the detection of a floating kidney. The absence of a movable kidney in this case eliminated such a diagnosis.

*Cholangitis, Cirrhosis and Hepatitis.* The primary nature of cholangitis in some cases was pointed out by Judd and McIndoe.<sup>11</sup> This condition may progress to an obliterative process, giving the picture of stricture in the common bile duct with jaundice, or it may progress upward into the liver and lead to hepatitis or cirrhosis. Cholangitis may be the chief lesion in some cases; in others extensive hepatitis and cirrhosis is the predominant lesion. Weir and Partch<sup>12</sup> state that colicky pains occurred in more than 40 per cent of their cases. Jaundice often recurred repeatedly and chills, fever and sweats were not uncommon.

Negative biliary drainages, normal liver function tests, negative Van den Bergh reaction, and normal icterus index excluded the above as a possible cause.

*Stricture of the Common Bile Duct.* Most of the strictures occur postoperatively and follow upon cholecystectomy, choledochostomy, or both. In 50 per cent of the cases there is painless jaundice and in 40 per cent of the cases there is typical colic and jaundice.<sup>12</sup>

The absence of jaundice excluded this condition.

*Carcinoma of the Pancreas.* Pain is a common symptom and may or may not be associated with jaundice. If the head of the pancreas is involved, jaundice usually occurs early, whereas if the tail or body is primarily involved it occurs much later and pain is an early and more prominent symptom. Weir

and Partch report that colic typical of gall-stone occurred in five of their cases.

Because of the positive Gruskin test, carcinoma of the body or tail of the pancreas had to be considered.

A consideration of these facts led to the conclusion that we were probably dealing with carcinoma either of the gall-bladder or of the pancreas, and normal sedimentation rate and the absence of anemia suggested that the process was still in an early stage. We were cognizant of the fact that cancer of the gall-bladder, in about 80 per cent of the instances, occurs in association with gall-stones and the absence of stone tended to diminish the positiveness of such a diagnosis. Immediate operation was advised and the patient was admitted to the Babcock Surgical Ward. Operation was performed by Dr. Burnett September 24, 1931. His report follows:

The gall-bladder is whitish in color, only very slightly thickened, relaxed, and empties readily on pressure. No stones palpable. The cystic duct is not enlarged. The common duct is normal to palpation. The liver shows slight fibrosis and its edge is very slightly thickened. *Stomach:* The omentum is plastered over the lesser curvature. Underlying this area is a large mass saddling the lesser curvature; straightened out, the mass is about 10 by 4 centimeters. It lies about four centimeters proximal to the pylorus and extends to within six centimeters of the cardia. The mass has everted edges and feels like a malignant growth. No nodules are present in the gastro-hepatic omentum. Reexamination of the liver shows no metastatic deposits to be present. The pancreas feels normal to touch and there is no evidence of fibrosis or growth.

The operation consisted of a gastric resection. The duodenum was partially mobilized and then resected below the pylorus and the distal end closed with Pagenstecher suture,

inverted and the adjacent mesentery ligated over the stump which was dropped; the jejunum was brought up and, at a point about fifteen centimeters from the ligament of Treitz, was anastomosed to the remnant of the stomach after the latter had been amputated on a radical line about three centimeters below the esophageal junction on the lesser curvature.

#### PATHOLOGICAL REPORT

*Gross Description.* The specimen is a rectangular piece of tissue 12 by 10 by 1 centimeters, removed from the wall of the stomach. In the central area, the continuity of the mucosal surface is broken and replaced by an ulcerative lesion 8 by 6 centimeters. The lesion is irregular in outline; its borders extend 1.6 centimeters above the mucosal surface and are hardened and eburnated. The base of the lesion is pale gray, rough, dull and moist. The surrounding mucosal folds are pink, moist and glistening; these too are thickened and hypertrophied. The external surface is rough, moist and glistening. Remnants of the mesentery are attached.

*Microscopic Description.* The mucosa is very much thicker than normal. On the inner surface there is a hyaline, structureless, mucus-like substance. The tubules are long and somewhat branched. Many mononuclear leukocytes lie in the tunica propria and there are a number of large lymph-follicles lying just above the muscularis mucosa. One end of the section, representing the edge of the ulcer, possesses tubules that are much less regular and very much more deeply stained than their fellows at the opposite end. About them, the leukocytic infiltration is intense. Everywhere beneath the muscularis there are masses of large, irregular, deep-staining cells with large reticular nuclei and pale-staining nucleoli. By higher magnification, many mitotic figures may be seen and it is noted that the cells are arranged somewhat in the form of glands. The reproduction is very crude. This cellular process is found even in the serosa.

*Diagnosis.* Carcinoma of the stomach.

#### COMMENT

The presence of carcinoma of the stomach in this case was an unexpected

finding, because to our knowledge attacks of pain resembling gall-stone colic have never been ascribed to cancer of the stomach and because none of our methods of study pointed to any gastric involvement. It demonstrated that gastric cancer may exist at a stage where none of our usual methods of study may give even suggestive information. Balfour<sup>13</sup> informs us that by actual study 50 per cent of all cancers of the stomach are absolutely hopeless when seen by physicians in the Mayo Clinic, and one-half of the remaining 50 per cent are explored surgically and found hopeless. This means that only 25 per cent of all cancers of the stomach are within the possible reach of our best methods of treatment. Of all the diagnostic methods at our command the positive Gruskin reaction was the only one that detected the fact that we were dealing with malignancy. It was only our previous experience with malignancy-positive Gruskin reactions that warranted us to regard such a report with respect. That a malignant growth was present, even though the stomach had not been suspected, indicated that in the Gruskin reaction we have a method for the diagnosis of cancer that merits our attention.

Such a case is of interest because it once more compels us to ask ourselves how we are to diagnose the early case of gastric carcinoma. All of our present methods of investigation evidently are of little value in the diagnosis of cancer of the stomach at its incipient stage. The gastric analysis at the very earliest stage of the condition will reveal nothing. There is a latent period between the beginning of the carcinoma and the onset of symptoms. Radical

extirpation of the mass, at this stage, will result in cure. Our problem is to diagnose our cases in this latent stage. When gastric carcinoma produces the symptoms which we are taught are characteristic of carcinoma, then the condition has reached the inoperable stage. Palpable tumor mass, achlorhydria, lactic acid, Oppler-Boas bacilli mean that extension has occurred; anemia and cachexia imply that there is toxemia. It is necessary to emphasize that the early lesion of gastric carcinoma can exist in the presence of apparently perfect health.

Of all the methods at our disposal at the present time roentgen-ray examination stands preëminent in the diagnosis of cancer of the stomach. A positive roentgen diagnosis, however, can be made only if there is a defect present producing an anatomic alteration in the gastric contour. Roentgen-ray examination is very likely to fail us in the early stage of gastric carcinoma before a well developed lesion has occurred. When a defect has occurred 96 per cent of the cases, we are told, can be diagnosed in skillful hands by roentgen-ray.

Gastric analysis is practically of no value in the early stage of the disease. At this phase in its evolution there has as yet occurred no reduction in the gastric secretory output and the figures for both the free and total acid values are within normal limits. There may even be a slight increase in acidity at this stage in an otherwise healthy stomach; this is due to the irritation of the growth or its toxins. There may also be high acid figures especially in prepyloric carcinomas in the early

stage and in the malignant forms of ulceration almost to the end.

When pus, muco-pus and blood are present in the gastric contents the lesion is already definitely established. Minute particles of tumor tissue may be found on lavage and are perhaps conclusive evidence, but this is a very uncommon finding in early cases.

The objection might be raised that stone in the common duct was not excluded. We are cognizant of the fact that common duct stone may occur without jaundice. Clute<sup>14</sup> reports that 39 per cent of the cases of common duct stone observed at the Lahey Clinic gave no history of jaundice in their previous attacks of pain and were not jaundiced at the time of operation. Judd and Marshall,<sup>15</sup> and Jordan and Weir<sup>16</sup> found that 20 per cent and 13.2 per cent of their cases respectively did not show jaundice before operation or at any time in their past history. Because of these facts the common duct should be explored more frequently at operation. Clute states that it is now his practice to open and explore the common duct in every patient: if it is dilated and thickened, whether or not stones can be palpated and regardless of any history of jaundice; in all patients who have had attacks of jaundice with pain, whether or not the duct is enlarged; in all cases in which there is much thickening of the head of the pancreas. Because at operation the common duct was not enlarged or thickened, or the head of the pancreas fibrosed, because there was no past history of jaundice associated with pain and because of the repeatedly negative bile microscopy, it was felt that there

was no need, nor any justification in view of the amount of major surgery already performed, to open and explore the common bile duct in this case.

#### PROGRESS NOTES

It is now one year since the patient was operated upon and he has not had a single attack of colic since. If any cause, other than his gastric lesion, was responsible for his attacks of colic it is not unreasonable to assume that he should have had a return of his attacks during the past year. This, I feel, proves the association between his carcinomatous lesion and the recurring attacks of colic. The mechanism involved in the production of the colic, in this case, cannot be definitely accounted for. We still are not able to explain adequately the cause of pain in the gastrointestinal tract. A summary of our present knowledge of the pathways along which abdominal pain travels is given by Alvarez.<sup>17</sup> He states: "It seems now to be established that all afferent fibers in the sympathetic nervous system are connected with the posterior root ganglia of the spinal cord and are therefore no different from sensory nerves elsewhere in the body; they simply happen to travel in the same sheaths with bundles of sympathetic fibers. Most of those fibers which leave the upper part of the abdomen reach the spinal cord by way of the splanchnic nerves from the sixth to the ninth. In some persons the splanchnic nerves are connected also with the fourth, fifth, tenth, eleventh and twelfth segments of the dorsal cord. Blocking of the splanchnic nerves causes anesthesia of the visceral peri-

toneum and of the organs in the upper part of the abdomen.

"The vagus nerves carry so few sensory fibers that they can be ignored whenever efforts are being made to relieve abdominal pain. That these fibers are unimportant is shown by the fact that peritonitis is usually painless in the case of patients who have suffered injury to the upper part of the spinal cord, and by the fact that operations in the upper part of the abdomen can be done painlessly under splanchnic blocking.

"There are still other paths by which pain might conceivably leave the abdomen. One is by way of the ganglionated sympathetic chain, and the other is by way of the aortic plexuses and thence through the rami communicantes to the spinal cord in the upper dorsal region. That these sensory connections cannot be very important is shown by the fact already mentioned that when the spinal cord is severed in the upper dorsal region, disease in the abdomen usually runs a painless course."

The patient made an uneventful recovery following his operation. On leaving the hospital October 30, 1931 he weighed 115 pounds. November 16, 1931: His only complaint is weakness. Weight 116 pounds. December 17, 1931: Still complains of weakness; no digestive complaints. *Gastric Analysis*—no free hydrochloric acid; total acid 2.5 at end of one hour. *Blood Count*—hemoglobin, 72 per cent, red blood cells 3,560,000, white blood cells 8100. *Sedimentation Rate*—average normal curve. *Van den Bergh*, direct negative; indirect 2 milligrams. *Icterus Index* 6. *Liver Function*—bromsulphalein (2 milligram dose) no retention at end of 30 minutes. *Galactose*—3.0 grams. *Gruskin Reaction*—only very faintly positive; not even a one plus. January 15, 1932: *Gruskin Reaction*—very faintly positive, slightly stronger than on December 17, 1931. Dr.

Gruskin thinks he may be starting on a recurrence of his carcinomatous lesion. March 20, 1932: *Gruskin Reaction*—positive reaction, plus one. May 16, 1932: *Gruskin Reaction*—positive, plus one. June 15, 1932: *Gruskin Reaction*—positive, plus two. *Blood Count*—hemoglobin, 74 per cent red blood cells 4,010,000, white blood cells 8450. *Sedimentation Rate*: almost horizontal line. Feels stronger, is able to be at work for a few hours daily. Weight 118 pounds. Appetite good. No digestive complaints. Fluoroscopic examination discloses no delay in the passage of the barium meal and consequently no recurrence with obstructive phenomena. August 3, 1932: *Gruskin Reaction*—plus two. Complaints of weakness. Appetite fair. Weight 117 pounds. September 21, 1932: Had two weeks vacation and feels stronger; complaint now is not of weakness but of fatigability on exertion. Appetite good. No digestive discomforts if he eats small meals. Weight 118 pounds. Gruskin reaction same.

The persistence of a positive Gruskin reaction in this case is in all probability due to lymph node involvement. The regional lymphatic structures are large factors in the treatment of gastric carcinoma. To quote Balfour<sup>13</sup>: "There are two facts of great importance regarding enlarged lymph nodes in cancer of the stomach: (1) enlargement does not necessarily mean involvement by cancer, and (2) a patient may be cured even if all involved lymph nodes are not removed. The first fact is well known and undisputed and its practical importance is that it impels the surgeon to avoid the mistake of assuming

incurability because of marked and extensive enlargement of regional nodes, a fact to which W. J. Mayo early drew attention. The second point is less easily substantiated, but sufficient examples are found in this series of cases of cured patients, in which the surgeon considered the resection only palliative because of incomplete removal of an involved chain of lymph nodes. I believe it to be a possibility that in cancer in any situation, removal of the primary growth and of the immediately adjacent lymphatic structures may bring about a permanent cure even if involved lymph nodes are left; the remaining nodes in such cases act as a sufficient barrier to further dissemination of the disease. It is, therefore, occasionally good practice to disregard involvement of lymph nodes if the primary growth can be removed, and to remove the adjacent lymphatic structures as completely as possible."

#### CONCLUSIONS

1. Our present methods of study are often inadequate for the diagnosis of carcinoma of the stomach in its incipient stage.

2. In the Gruskin reaction we have a test for the diagnosis of malignancy that merits our attention.

3. Carcinoma of the stomach may produce attacks of pain indistinguishable from those of cholelithiasis.

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## The Poet of Flanders Fields\*†

Lieutenant Colonel John McCrae, Canadian Army Medical Corps

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THE soldier poet who wrote the most arresting poem of the World War was Canadian, born of Scottish ancestry. He was the second son of David McCrae and Janet Eckford who were married January 21, 1870. The older son Thomas McCrae also became a notable man, a professor of medicine, the relative by marriage of Sir William Osler with whom he collaborated in the production of an encyclopedic treatise on medicine well known to most practitioners.

John was born November 30, 1872. He began his education when scarcely three years of age by learning the Shorter Catechism. This learning of the Catechism in what might almost be termed infancy, was a sort of test applied by many Scottish families to determine if the child were capable of becoming a scholar. If he passed the test successfully he was marked for the university and one of the learned professions, divinity, medicine or the

law. It is said on no less authority than that of Sir Walter Scott that it was the ambition of every Scottish mother to have her son "wag his head in a pulpit", and failing that to become a physician or an advocate.

Having passed the Catechism test, and having no doubt learned from it at so early an age that "He should renounce the devil and all his works, the pomps and vanities of this wicked world", as that noble and earnest document recommends for us to do, he in due time went to the grammar school and the high school. In 1888 he entered the University of Toronto with a scholarship, and graduated from the Faculty of Arts in 1894 with the Bachelor of Science degree, his major being in biology. He graduated in medicine and surgery in 1898, a gold medallist, with a scholarship in physiology and pathology. He entered immediately upon his internship in Toronto General Hospital. He had spent the previous summer between his junior and senior year at the Garrett Children's Hospital in Mt. Airy, Maryland. In 1899 he went to Johns Hopkins Hospital as a resident physician and then to McGill University as an assistant in pathology and assistant pathologist to the Montreal General Hospital.

At this point, however, his work was

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†This is the fifth of a series of portraits of medical poets. Those which have previously appeared in the ANNALS OF INTERNAL MEDICINE are:

Joseph Rodman Drake—February, 1929.

Oliver Wendell Holmes—June, 1930.

Oliver Goldsmith—May, 1932.

Wm. Savage Pitts—January, 1933.



DR. MCCRAE AND BONNEAU

interrupted by the Boer War. In addition to medicine he had two other major interests, poetry and military life. His father had been a militia officer, and at fourteen years of age John had joined the Guelph Highland Cadets. Now as a lieutenant of Canadian Artillery and a section commander he went out to South Africa on the

*Laurentian*. Here is one of his first letters from the war:

Van Wyks Vlei  
March 22, 1900

Here I am with my first command. Each place we strike is a little more God-forsaken than the last, and this place wins up to date. We marched last week from Victoria west to Carnovan, about eighty miles. We stayed there over Sunday, and on Monday my sec-

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tion was detached with mounted infantry, I being the only artillery officer. We marched fifty-four miles in thirty-seven hours with stops; not very fast, but quite satisfactory. My horse is doing well, although very thin. Night before last on the road we halted, and I dismounted for a minute. When we started I pulled on the lines but no answer. The poor old chap was fast asleep in his tracks, and in about thirty seconds too.

This continuous marching is really hard work. The men at every halt just drop down in the road and sleep until they are kicked up again in ten minutes. They do it willingly too. I am commanding officer, adjutant, officer on duty, and all the rest since we left the main body. Talk about the Army in Flanders! You should hear this battalion. I always knew soldiers could swear, but you ought to hear these fellows. I am told the first contingent had got a name among the regulars.

Here is another note of war and of a commander whose name is a byword in the British Army.

We were inspected by Lord Roberts. The battery turned out very smart, and Lord Roberts complimented the Major on its appearance. He then inspected, and afterwards asked to have the officers called out. We were presented to him in turn; he spoke a few words to each of us, asking what our corps and service had been. He seemed surprised that we were all Field Artillery men, but probably the composition of the other Canadian units had to do with this. He asked a good many questions about the horses, the men, and particularly about the spirits of the men. Altogether he showed a very kind interest in the battery.

At nine took the Presbyterian parade to the lines, the first Presbyterian service since we left Canada. We had the right, The Gordons and the Royal Scots next. The music was excellent, led by the brass band of the Royal Scots, which played extremely well. All the singing was from the psalms and paraphrases: "Old Hundred" and "Duke Street" among them. It was very pleasant to hear the old reliables once more. "McCrae's Covenanters" some of the officers

called us; but I should not like to set our conduct up against the standard of those austere men.

A veteran of the South African War, and with the Queen's Medal with clasps, he returned to Montreal to resume his practice, his place as a promising young pathologist, his teaching, his military drill, and his poetry. He was appointed physician to the Alexandria General Hospital, assistant physician to the Royal Victoria Hospital and a lecturer at the University. Eventually he became a fellow of the Royal College of Physicians and built a solid reputation as both a pathologist and an internist. He published a number of papers and at the time the World War began was finishing the revision of Adami's great *Textbook of Pathology*.

As early as 1894 he had begun to publish poetry, when two short poems "The Shadow of the Cross" and "The Hope of My Heart" appeared in the *Varsity*. In 1895 "Unsolved" was contributed to *The Canadian Magazine*. From then on until his death, *The Spectator*, *University Magazine*, *The Canadian Magazine* or the *West Minister* published nearly every year some verse by him. His contributions were not many, scarcely one or two a year, all short, and all similar in form and character. The usual or most common verse form was one called by the student of prosody the rondeau, and McCrae studied and experimented with this form until he was letter perfect in its use as a vehicle of poetic expression. The themes of his poetry were death, duty, and regret for lost love and life. It is possible that he was influenced by Houseman whose "Shropshire Lad", "that wonderful burst of song" as someone has called it, had

appeared in 1896. The elegiac note, the lament for loss is particularly a prominent feature of both poets.

One of the best of the poems is "Quebec" published in the *University Magazine* in 1908 on the occasion of the Tercentenary of the City.

#### QUEBEC

1608      1908

Of old, like Helen, guerdon of the strong—

Like Helen fair, like Helen light of word,—

"The spoils unto the conquerors belong.

Who winneth me must win me by the sword".

Grown old, like Helen, once the jealous prize

The strong men battled for in savage hate,

Can she look forth with unregretful eyes,

Where sleep Montcalm and Wolfe beside her gate?

"The Oldest Drama" from the *University Magazine* of 1907, "Upon Watts' Picture 'Sic Transit'", *University Magazine* 1904, "Isandlwana", *University Magazine* 1910, represent some of the best of his poetic work during the years of busy professional life.

He was a member of the Pen and Pencil Club of Montreal, a group of young writers and artists. He was popular socially and went about to social gatherings. He went fishing on his vacation and he made a number of journeys to Europe and the United States. How a fine looking and successful young doctor, five feet eleven inches tall, weighing one hundred and eighty pounds, and a poet, in fact in every respect the most eligible of bachelors, contrived to remain a bachelor during these years is difficult to understand, but he managed to do so, and in fact never married.

When the World War began in 1914 McCrae was in England but he at once

returned to become Brigade Surgeon to the First Artillery Brigade. Nearly his whole service before the World War, including the South Africa War, had been as a combat officer of artillery and he never quite got over a desire to continue as a line officer. He had plenty of war, however, as a medical officer, as these notes from two of his letters indicate:

Sunday, April 25, 1915.

On the front field one can see the dead lying here and there, and in places where an assault has been they lie very thick on the front slopes of the German trenches. Our telephone wagon team hit by a shell; two horses killed and another wounded. I did what I could for the wounded one, and he subsequently got well. This night, beginning after dark, we got a terrible shelling, which kept up till two or three in the morning. Finally I got to sleep, though it was still going on. We must have got a couple of hundred rounds, in single or pairs. Every one burst over us, would light up the dugout, and every hit in front would shake the ground and bring down small bits of earth on us, or else the earth thrown into the air by the explosion would come spattering down on our roof, and into the front of the dugout. Col. Morrison tried the mess house, but the shelling was too heavy and he and the adjutant joined Cosgrave and me, and we four spent an anxious night there in the dark. One officer was on watch "On the bridge" (as we called the trench at the top of the ridge) with the telephones.

Thursday, May 27, 1915.

Day cloudy and chilly. We wore our greatcoats most of the afternoon, and looked for bits of sunlight to get warm. About two o'clock the heavy guns gave us a regular "blacksmithing". Every time we fired we drew a perfect hornet's nest about our heads. While attending to a casualty, a shell broke through both sides of the trench, front and back, about twelve feet away. The zigzag of the trench was between it and us, and we escaped. From my bunk the moon looks

down at me, and the wind whistles along the trench like a corridor. As the trenches run in all directions they catch the wind however it blows, so one is always sure of a good draught. We have not had our clothes off since last Saturday, and there is no near prospect of getting them off.

Here is one with an observation by the poet doctor that was later to appear in "Flanders Fields":

and in the sky  
The larks, still bravely singing, fly  
Scarce heard amid the guns below.

Monday, April 26, 1915.

Another day of heavy actions, but last night much French and British artillery has come in, and the place is thick with Germans. There are many prematures (with so much firing) but the pieces are usually spread before they get to us. It is disquieting, however, I must say. *And all the time the birds sing in the trees over our heads.*

His horse's name was Bonfire and his dog's Bonneau. He wrote clever little notes as if from these animals, and signed those from the horse with a horseshoe as "Bonfire His Mark". References to animals and to trees and flowers are frequent in his letters and show his great interest in them.

"In Flanders Fields" appeared in *Punch* in the spring of 1915. Major General E. W. B. Morrison, who was in command of the brigade in which Major McCrae was serving, has in a letter described so well the actual circumstances under which the poem was written that his description is reproduced here:

"This poem", General Morrison writes, "was literally born of fire and blood during the hottest phase of the second battle of Ypres. My headquarters were in a trench on the top of the bank of the Ypres Canal, and John had his dressing station in a hole dug

in front of the bank. During periods in the battle men who were shot actually rolled down the bank into his dressing station. Along from us a few hundred yards were the headquarters of a regiment, and many times during the sixteen days of battle, he and I watched them burying the dead whenever there was a lull. Thus the crosses, row on row, grew into a good-sized cemetery. Just as he describes. We often heard in the mornings the larks singing high in the air, between the crash of the shell and the reports of the guns in the battery just beside us. I have a letter from him in which he mentions having written the poem to pass away the time between the arrival of batches of wounded, and partly as an experiment with several varieties of poetic meter. I have a sketch of the scene, taken at the time, including his dressing station; and during our operations at Passchendaele last November, I found time to make a sketch of the scene of the crosses, row on row, from which he derived his inspiration."

Here is the poem:

#### IN FLANDERS FIELDS

In Flanders fields the poppies blow  
Between the crosses, row on row,  
That mark our place; and in the sky  
The larks, still bravely singing, fly  
Scarce heard amid the guns below.

We are the Dead. Short days ago  
We lived, felt dawn, saw sunset glow,  
Loved and were loved, and now we lie  
In Flanders fields.

Take up our quarrel with the foe;  
To you from failing hands we throw  
The torch; be yours to hold it high.  
If ye break faith with us who die  
We shall not sleep, though poppies grow  
In Flanders fields.

In the early summer after the sec-

ond battle of Ypres, the poet, now made famous overnight, was detached from the First Artillery Brigade and ordered for duty as Chief of the Medical Service at No. 3 General Hospital at Boulogne. At about this time also he was recommended for promotion to Lieutenant Colonel. He had many regrets at leaving the guns, but his services as an internist were of much greater value, and every medical man with specialist training was needed in the hospital now filled with sick and wounded after the desperate winter of 1915. He remained as Chief of Medicine until 1918 when he was selected to command General Hospital No. 1, but before he could assume this command it was proposed that he should be appointed "Consultant Physician to the British Army in the Field". He was never to receive either appointment. He contracted pneumonia and died at General Hospital No. 14 after an illness of only five days.

Each great war has furnished the inspiration for some great poem. There is little doubt but that "In Flanders Fields" is the poem of the World War that will linger longest in the minds of men. Its title, its simplicity, its easy measure, and its combination of elegy and call to duty are reasons for its sudden and wide publicity. With a music hall song, "It's a Long Long Way to Tipperary", it shares the honor of expressing best in fewest words the World War atmosphere and mood.

McCrae's scientific papers are well written, and his editing of Adami's Pathology well done. But there is one

short piece of prose that is more than well written and constitutes a fitting tribute to himself as well as being worthy to be considered beside the three other great tributes to the medical profession, namely the self-imposed Oath of Hippocrates with its lofty ethics, the well known eulogy by Robert Louis Stevenson, and Sir William Osler's address in which he refers to medicine as "a calling not a trade". Compare these with John McCrae on the legend from Watts' picture "Sic Transit", the subject of one of his earlier poems, and it stands the test well. Here is what he says of this profession: "What I spent I had: What I saved I lost: What I gave I have." "It will be in your power every day to store up for yourselves treasures that will come back to you in the consciousness of duty well done, of kind acts performed, things that having given away freely you yet possess. It has often seemed to me that when in the Judgment those surprised faces look up and say, 'Lord, when saw we Thee anhungered and fed Thee; or thirsty and gave Thee drink; a stranger, and took Thee in; naked and clothed Thee'; and there meets them that warrant-royal of all charity, 'Inasmuch as ye did it unto one of the least of these, ye have done it unto Me,' there will be amongst those awed ones many a practitioner of medicine."

#### BIBLIOGRAPHICAL NOTE

Most of the material for this article was obtained from Sir Andrew Macphail's tribute to Colonel McCrae, written in 1919, to accompany a collected edition of his poems.

## Editorial

### *CERTAIN FACTORS IN THE LOCALIZATION OF DISEASE*

The individuality of the various clinical forms of disease depends largely upon the tendency each exhibits to localize differently in the human tissues. The external specificity of symptoms and signs observed by the clinician corresponds to an internal specificity of pathological lesions or of functional disturbances. The factors entering into the determination of the specific localization of disease are to a large extent still obscure though from the earliest times they have been the subject of medical investigation.

In recent years there has been a renewal of activity in the study of the influence of heredity on the occurrence of disease. In addition to the well known hereditary anatomical anomalies it has been shown that certain of the heredo-familial degenerative diseases of the nervous system and certain metabolic disturbances such as pentosuria and alkaptonuria can be definitely followed as gene-determined characteristics. The list of such diseases is a large and important one. The lesions, especially in the diseases of the sense organs of the central nervous system, are as a rule exquisitely localized. Heredity is then an important factor which by as yet unknown mechanisms localizes disease of endogenous origin to specific sites in the tissues of the body.

Less definite in its findings has been the modern reinvestigation of the effects of constitution upon disposition to the various diseases. Borchardt defines constitution as the status of the organism as conditioned by both heredity and environment. It is the aggregate of those characteristics, anatomical, physiological, and psychical which constitute the total individual. Various types of constitution have been described such as the slender or asthenic type and the broad or pyknic type. These separate types of constitution have been shown to exhibit a difference in their disposition to many diseases such as tuberculosis, gout, diabetes, gall-stones, asthma, peptic ulcer, etc. In some instances these variations in disposition seem to be linked with variations in physiological functions which might be causative. For the most part, however, constitutional pathology does not offer explanations of its findings. It is in the descriptive rather than in the elucidative phase of its development. We may accept the fact that constitution to some extent determines the localization of disease in the body.

The study of these more general phenomena, heredity and constitution, has been accompanied in our day by an attack on the problem of disease localization carried on from quite a different angle. The investigations to which we refer have dealt with the more intimate mechanisms by which

local tissue immunity or susceptibility are determined. These studies have been concerned chiefly with the problems connected with the localization of the infectious diseases, and with the localized effects of toxins, drugs, and poisons.

The degree to which bacteria are invasive has long been conceded to be the result of a balance between two opposing factors: the "virulence" of the bacterial species and the resistance of the host.

Virulence is at best a vague, all inclusive term used to cover the sum total of all the harmful effects of a bacterial species. Included in it is the power of a particular strain to attack successfully highly localized areas within the body of the host. To an increasing extent in recent years this specificity of effect of certain bacterial strains has won recognition and the bitter opposition which met Rosenow's pioneer work in this field has to some extent died away. The problem of bacteriology is now to determine in how far tissue specificity shown by pathogenic organisms is related to the specificity of the types into which the bacterial species *in vitro* can be subdivided. These types until recently could be considered specific only upon the basis of specific immunologic responses incited by their injection. The brilliant researches of Avery and his co-workers have given us evidence in the case of the pneumococcus, that type specificity and virulence are alike functions of the capsule of the organism, and that the capsule of each type of pneumococcus contains a polysaccharide which is chemically and immunologically distinct from that contained in the capsule of

the other types. Such light thrown upon the nature of type specificity within the bacterial species must serve in time to enlarge our understanding of the mechanism of tissue specificity of bacterial action in the body, with a consequent expansion of our knowledge of the factors in the localization of the bacterial diseases.

The relationship of the chemical constitution and physical state of a substance introduced into the body to the localization of this substance in the organs of the body was studied intensively by Ehrlich and led directly to his bold conception of union by chemical affinity between protoplasm and the injected drug or dye or toxin. He was led by this conception to search for specific drugs which would be toxic to parasites and possess a strong chemical affinity for them, while showing only a weak chemical affinity for the tissues of the host. Such a substance could be administered in sufficient dosage to kill the infecting organism and leave the host unscathed. The enunciation of the theory of chemotherapy has been enormously valuable because of the stimulation it gave to the synthesis of large series of new chemical compounds and to their trial as therapeutic agents. The attempt to explain their distribution and action on the basis of chemical affinities has met with difficulties which have somewhat blurred the simple outlines of the original theory. A further difficulty and disappointment of the chemotherapeutic era has been the repeated demonstration of the fact that the parasitocidal action of a chemical substance *in vitro* very often does not correspond to its action on the parasite in the animal body. The orig-

inal compound introduced may be altered by oxidation, reduction, or synthesis in the body and it may be only the end product of such reactions that is available for chemotherapeutic action. It has been found also that the effectiveness of certain drugs seems to be as an adjuvant to the immune reactions of the host and that the optimum dose for this joint action lies well below the maximal dose which would be tolerated. Perhaps the essence of the difficulty in chemotherapeutic research lies in the fact that whereas the chemical constitution of the prepared remedy is known, the nature of the physicochemical medium in which it must act, and the chemical nature of the parasitic or host protoplasm with which it is intended to join, are both still obscure. A large measure of empiricism must prevail in chemotherapy while it still deals with such unknown factors. It may be that the separation of the chemical fractions of microorganisms, a line of investigation which in the hands of Heidelberger and others has revealed the chemical compounds responsible for the type characteristics of the pneumococci, will eventually simplify the task of chemotherapy by indicating the precise nature of the substance on which the chemical remedy must act. A sound theory of the nature of the affinity which localizes the action of a drug or a toxin must await further knowledge.

These investigations which are attempting to reduce to terms of chemical constitution and physical state the attributes of bacteria and of drugs which give specificity to their biological behavior have been supplemented by studies bearing upon the variations in

resistance of the various tissues and organs of the host.

It is apparent that the exterior of the body of the host offers in different areas a variable degree of resistance to invasion, the basis of which lies in structural differences. The toughness and impermeability of the skin as compared to the delicacy and absorptive power of the mucous membranes, the heat and moisture in the folds of axillae and groins as compared with the hands, the differing degrees of exposure to trauma and friction, all such structural and functional differences in the exterior of the body are no doubt important factors in determining the localization of the portals of entry of the infections.

When the infection is within the body, however, and in process of dissemination through the blood stream, the factors which determine its secondary localizations in certain sites while leaving other parts uninvolved offer fascinating problems. It is reasonable to suppose that once within the closed system of the circulation, bacteria, drugs, toxins, or other foreign material will pass out again into the tissues at the points where the vascular wall is most readily permeable. The capillary wall towards the venous end of the capillary has been shown to be the most permeable portion of the vascular system. The nature of this permeability, and its control by the autonomic system, by hormonal action, and by the physicochemical constitution of the blood and tissues, have been intensively studied in recent years. Burrows has recently summarized our present knowledge of how local changes in

capillary permeability may lead to localization of disease, and has cited a vast number of experimental and clinical observations which indicate the actual importance of this factor.

The advance of our knowledge of capillary permeability has depended largely upon two methods: The visualization of the capillaries and the use of injections of dyes which by the greater intensity of staining make manifest the area in which permeability has been increased. By a combination of these methods it has been shown that increased permeability of capillaries may be quite independent of dilatation and even of stasis. Local inflammation, local ischemia, local increase in hydrogen ion concentration, local disturbance of vascular innervation, local action of histamine-like substances, may be accompanied by a local increase in capillary permeability as shown by a localization of injected dyes. Moreover, it has been shown that the capillaries in such an area may remain more than normally permeable for some time after the inciting cause has disappeared. These experimental observations with dyes throw light on the mechanism involved in certain further experimental studies dealing with the localization of disease.

The tendency of blood-borne infections to localize in traumatized areas has been repeatedly proven by experimental methods and corresponds closely to similar localizations of injected dyes. The normal brain and spinal cord always remain free from dye injected intravenously, but Macklin and Macklin found that if rats were injected with trypan blue and then given blows on the head this trauma was sufficient

to localize the dye in the brain as shown by a pronounced staining of the tissues. Okuneff applied a hot water bag to the abdomen of a rabbit and then gave an intravenous injection of trypan blue. As a result not only was the belly wall where it had been in contact with the hot water bag strongly colored, but so also were the subjacent coils of intestine. Ebbecke has reported that if trypan blue or trypan red be injected into the general blood stream and a wheal be then produced in the skin, the dye will discolor the wheal. Similarly Chesney, Turner and Halley excised pieces of skin from the backs of rabbits and later gave intravenously 0.1 c.c. of a testicular emulsion of active treponemes. At periods varying from nineteen to sixty-seven days subsequent to these injections every one of the dorsal scars became affected with indurated syphilitic lesions, whereas no other cutaneous lesions occurred. In humans the tendency for secondary syphilitic eruptions to be more intense about old scars, chronic ulcers, and areas of irritation has been repeatedly noted. The tendency of the lesions to be most numerous about old tattooing is especially striking. Krause injected cultures of tubercle bacilli intravenously into rabbits and then wrenched a joint. In one-half of these rabbits the injured joints became tuberculous. In septicemia due to typhoid bacilli, pneumococci, or staphylococci, secondary localizations at sites of trauma, of pressure, or even of hypodermic injections have been very frequently reported. In the experimental studies of the virus diseases various forms of irritation as a means of localizing the disease have been repeatedly employed

by many investigators. The virus of vaccinia when intravenously given will produce a vaccinal eruption wherever the skin has been traumatized. Flexner and Amoss found that infection of the nervous system with poliomyelitis virus given intravenously could only be obtained if enormous doses were employed. If, however, an intraspinal injection of foreign serum had been made twelve or eighteen hours beforehand, infection was readily established by giving virus intravenously.

A mass of experimental work, from which these few illustrative examples are drawn, points strongly towards the dominant rôle of local variations in capillary permeability as a factor in the localization of blood-borne diseases.

Beyond the capillaries lie the extracellular tissue fluids and the tissue cells. It is not sufficient that a noxious agent permeate the capillary endothelium; it must also exert its effect upon the extravascular tissues before evidence of

a localized lesion appears. Gay has discussed the variable resistance of the tissues to such invasion. Theoretically, he points out, successful local resistance might be due to local formation of antibody, or to a local accumulation of antibody formed elsewhere. He sets aside both hypotheses, however, and inclines to believe that local resistance is not humoral but chiefly cellular in character. In this connection he has brought forward evidence that a particular type of macrophage, the clasmatocyte, plays the chief rôle in local defense reactions and he suggests that the varied susceptibility to infection of different tissues depends chiefly upon the distribution among them of this macrophage.

Necessarily in this brief review many aspects of the localization of disease have not been mentioned. Enough perhaps has been said to indicate some of the recent lines of attack upon this fundamental problem of human pathology.

## Reviews

*Intracranial Tumors.* By PERCIVAL BAILEY, Professor of Surgery, University of Chicago. xx plus 475 pages, with 155 illustrations. Charles C. Thomas, Springfield, Illinois, 1933. Price, \$6.00.

This book comes at a very opportune time for students and those interested in the subject of intracranial tumors, because it is the first of its kind to present the whole subject from a much needed clinico-pathologic viewpoint. The material is presented in the readable style of informal clinics, which were amplified for publication. Fifty-nine illustrative cases from the author's clinic form the basis of the text.

The opening chapters include a discussion of the problem of tumors in general, the

modern classification of intracranial tumors, and valuable analytic tables. The more fundamental anatomic and physiologic conceptions are also reviewed. Each type of intracranial tumor is presented from the clinico-pathologic viewpoint, with emphasis on the latter. The author correctly stresses the view that it is no longer sufficient to know that a patient has a brain tumor and its location, but the histological type as well. Several clinical cases are given to illustrate each histological type. From case histories the clinical story of each individual type of tumor is developed. The general characteristics, the age incidence, the common location of the tumor, the gross appearance, and the microscopic anatomy are discussed. The his-

tory of the developing neoplasm is given by detailed review of symptoms and the resultant neurologic signs. Each tumor is described in the location in which it is most commonly found, with a discussion of the neurologic syndromes which result from neoplastic invasion of each cerebral subdivision. In the chapter on medulloblastoma, for instance, the syndrome of the vermis cerebelli is outlined; in connection with hypophyseal adenomas, acromegaly and the hypopituitary syndrome are discussed. Regional physiology and anatomy are included in the discussion of the neurologic signs and symptoms of each syndrome. A brief note concerning the accepted treatment is given for each tumor. Chapters on general diagnosis, differential diagnosis, and general treatment of intracranial tumors conclude the book.

The text is printed on dull paper and adequately illustrated with 155 pen-and-ink drawings. While reading is made easier by the use of dull paper, this is done at the expense of eliminating the usual and preferable half-tones. Photomicrographs would have added to the illustrations. The bibliography contains some four hundred references which serve as a valuable guide for supplementary reading. The book is exceptionally well done and deserves a place in the library of any one interested in intracranial tumors.

J. G. A., JR.

*Diseases of the Heart.* By SIR THOMAS LEWIS. 297 pages. The Macmillan Company, New York. 1933. Price, \$3.50.

This book is written in the author's usual clear and succinct style. It is purposely designed for use by practitioners and students, and will be of little value to one who is already primarily concerned in diseases of the heart. The subject is approached largely from the point of view of bedside observations, and these are clearly stated. The author has a particularly sane and common sense attitude toward the limitations of the usefulness of digitalis and toward the handling of patients suffering with essential hypertension. Many cardiologists would be more optimistic in regard to the usefulness of quinidine in the therapy of auricular fibrillation. There is perhaps too little discussion of the information to be obtained from

electrocardiography and other mechanical methods, and too great stress placed upon somewhat unreliable clinical methods. The reviewer certainly cannot agree with the following statement: "The fingers should be trained to recognize a high tension pulse; for a pressure meter can hardly be used as a routine in general practice." The discussion of those patients with complaints referred to the heart and who present no evidence of heart disease is inadequate. Such patients, both in their diagnostic and therapeutic implications offer serious problems for the practitioner. The author has dealt with them in a very short chapter on the "Effort Syndrome," and a paragraph or so on the occurrence of heart pain in neurasthenia, which latter term is apparently used as a sort of catch-all for neurotic invalidism. The reviewer sees little reason for not dealing with the "Effort Syndrome" in a chapter devoted to the psychoneuroses. However, because of its clarity and lack of extensive theoretical discussions, and because of the author's excellent clinical observations, and his conservative and common-sense approach to the whole subject, this should prove a valuable book for the general practitioner.

W. S. L., JR.

*Outline of the Cranial Nerves.* By JOHN FAVILL, A.B., M.D., F.A.C.P., Associate Clinical Professor of Neurology, Rush Medical College of the University of Chicago. Cloth. 120 pages. The University of Chicago Press, Chicago, Illinois. 1933.

This little book should be of decided value to the medical student or to any one interested in the study of Neurology. Each cranial nerve is treated under five headings: anatomy, function, tests, pathology and localization, thus bringing together facts that are usually not found under one classification. The chapter relating to the eighth nerve is especially good—giving a full account of the vestibular tests and their significance.

Considered as a whole, this is an excellent summary of our present day knowledge of the cranial nerves.

A. C. G.

*Clinical Aspects of the Electrocardiogram.* By HAROLD E. B. PARDEE, M.D. Third edition, revised. 295 pages. Paul B. Hoe-

ber, Inc., New York. 1933. Price, \$5.50.

The third edition of this book has been revised and somewhat amplified. The author has accepted the newer views in regard to the localization of premature ventricular beats and of the myocardial lesions giving rise to bundle branch block and has revised his terminology accordingly. The chapters on changes in the electrocardiogram due to myocardial disease, and the clinical significance of abnormal waves should be of general interest. The author happily points out that while certain of such changes undoubtedly mean temporary or permanent serious myocardial disease, and others probably indicate abnormalities of the myocardium, one is not justified in making a prognosis upon the electrocardiogram alone. One too often sees patients who have been frightened unjustifiably by a diagnosis of myocardial disease based upon slight deviations of uncertain meaning from the normal electrocardiogram. Ventricular axis deviation and the arrhythmias are adequately covered and there is a clear exposition of the theory of the electrocardiogram. The two types of electrocardiograph are described and the technic of their use explained. The book should be readily understood by the practitioner of medicine and should be of value also to those primarily interested in heart disease.

W. S. L., Jr.

*Procedure Book of the Methodist Episcopal Hospital.* 2nd Edition. Brooklyn, New York, 1932.

This small volume is a paper bound book of two hundred and one printed pages, containing twenty-five chapters and an index. Between each chapter there are six blank pages for additional notes. Its size, 6 x 9 inches, precludes the possibility of its being carried about in the pocket.

Originally prepared to serve the undergraduate nurses of the Methodist Episcopal Hospital, the book has been expanded in this edition to be of service also to the interne staff. All printed procedure books are of interest to the superintendents, heads of training schools, chiefs of services, and house officers of other hospitals. They contain much valuable information which can be taken over to serve in the construction of

new procedure books. This little volume is quite complete and contains a vast amount of useful data. One strange omission is the lack of any mention of blood transfusions. It is also of interest, though not important, that though the junior nurses are specifically forbidden to sing, whistle, or play musical instruments, no mention of the rules as to smoking is made.

M. J. A.

*Diseases of the Eye.* By HOFRA ERNST FUCHS. Revised by MAXIMILIAN SALZMAN. Translated by E. V. L. BROWN. Tenth English Edition. 255 illustrations and 41 colored figures. J. B. Lippincott Company, Philadelphia. 1933. Price, \$7.00.

This volume, which constitutes the tenth English edition of Fuchs' famous *Textbook of Ophthalmology*, has been reduced approximately one-third in the number of pages as compared with recent editions. The lessened size is due largely to the elimination of Part I of the former work consisting of Chapter one (Objective Examination of the Eye) and Chapter two (Functional Testing), Part III which took up anomalies of Refraction and Accommodation, and Part IV which gave a concise description of the various operations upon the eye and its adnexae.

There has also been a considerable rearrangement of the subject matter. Part I treats of the Lids and Conjunctiva; Part II, Diseases of the Tunica Fibrosa (Cornea and Sclera); Part III, Diseases of the Uvea; Part IV, Diseases of the Retina and of the Optic Nerve; Part V, Diseases of the Lens, Zonule and Vitreous; Part VI, Diseases of the Eyeball as a Whole; Part VII, Diseases of the Orbit and Part VIII, Diseases of the Nerves of the Eye.

While the rearrangement of material may be an advantage and the elimination of Parts I, III, and IV may be gratifying to the undergraduate, these changes certainly will not be pleasing to the postgraduate student who has looked upon his Fuchs' as his Ophthalmic Bible.

It would seem that greater attention should have been directed to the use of the slit-lamp in determining microscopic changes in the living tissues, as an aid to diagnosis. The reviewer also believes that greater attention should have been given to the therapeutic use

of tuberculin in the treatment of the various tuberculous lesions. The modern conception and treatment of retinal detachments could also be made more explicit.

In spite of the somewhat limited scope, the book is still a very valuable work upon the diseases of the eye. C. A. C.

*Criteria for the Classification and Diagnosis of Heart Disease.* By The Criteria Committee of the Heart Committee of the New York Tuberculosis and Health Association, Inc. New York Tuberculosis and Health Association, New York. 131 pages. 1932.

One can only be in sympathy with the purpose of this publication. It should serve as an important step towards the adoption of a uniform nomenclature for heart disease, and uniform criteria for using such nomenclature. The book deals with etiological, anatomical and physiological diagnosis, and the functional state of the heart. In the appendix are sections on electrocardiography and radiography. It is not a clinical exposition of heart disease, but as an aid in classifying cases it should prove most valuable to any physician interested in internal medicine.

W. S. L., JR.

*The Doctrine of the Healing Power of Nature Throughout the Course of Time.* By MAX NEUBURGER, M.D., Ph.D., Professor of History of Medicine of the University of Vienna. Translated by LINN J. BOYD, M.D., F.A.C.P., Professor of Pharmacology, The New York Homeopathic Medical College and Flower Hospital. Paper. 184 pages. 1933.

To those interested in the history of medicine, particularly from its philosophical aspects, this monograph by one of the world's greatest medical historians should be of considerable interest. The doctrine of the healing power of nature has occupied the attention of the physician for thousands of years. Today, it is probably of greater importance than at any time in the past. Our studies of the internal secretions and of immunity have brought the matter to the forefront. Dr. Neuburger traces the history of this subject from the days of Hippocrates, when the occurrence of spontaneous healing was established as a fact for the first time, through the ages down to modern times.

Dr. Boyd's translation is excellent.

A. C. G.

## College News Notes

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. W. R. Brooksher (Fellow), Fort Smith, Ark.—2 reprints;

Maj. Leon A. Fox (Fellow), Washington, D. C.—2 reprints;

Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;

Dr. Oliver T. Osborne (Fellow), New Haven, Conn.—1 reprint.

Dr. Arthur L. Bloomfield (Fellow) has been appointed Acting Dean of Stanford University School of Medicine, San Francisco. Dr. Bloomfield is also Professor of Medicine and Secretary of the School.

Dr. John Severy Hibben (Associate), Pasadena, Calif., has been appointed Chairman of a Special Committee on Physical Therapy of the California State Medical Association to survey the present practice of physical therapy with reference to education and practice, and to report on it at the next meeting of the State Medical Association.

Dr. Walter L. Bierring (Fellow), Des Moines, Iowa, has been appointed State Health Commissioner for Iowa, beginning July 1.

Dr. Maxim Alexander Oginsky (Fellow), formerly Medical Director and Pathologist to the Saratoga Hospital at Saratoga Springs, N. Y., was appointed April 1, 1933, as Di-

rector of Laboratory and Pathologist to the Woman's Hospital, Detroit, Mich.

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Dr. James A. Lyon (Fellow), Washington, D. C., and Dr. Lewis C. Ecker (Associate), Washington, D. C., are President and Vice-President, respectively, of the Washington Heart Association.

Dr. Lawrason Brown (Fellow), Saranac Lake, N. Y., was recently reelected President of the Saranac Lake Society for the Control of Tuberculosis.

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Dr. William S. Rude (Fellow), Ridgely, Tenn., was recently elected one of the Vice-Presidents of the Tennessee State Medical Association.

### OBITUARIES

#### DR. MARTIN JAMES LARKIN

Dr. Martin James Larkin (Fellow), Toledo, Ohio, died March 11, 1933; aged 39 years. On the evening of July 9, 1932, while on his way to the Mercy Hospital, he was apprehended by a man who demanded his car. While he was in the act of leaving his car, the gunman opened fire on him. The bullet entered the left side of the face, fractured the mandible, passed through his mouth and lodged in the neck, opposite the transverse processes of the second and third cervical vertebrae. Dr. Larkin recovered from the wound; the fractured mandible united and he apparently returned to normal, so that he returned to practice on January 3, 1933. On January 18, he complained of pain in the cervical region. Two days later an abscess was evacuated, and one week later the bullet was removed. Several days later he gave signs of cerebral irritation and of blood stream infection. His condition became progressively worse, and he expired on March 11, 1933.

Dr. Larkin was a graduate of St. John's University, Toledo, receiving the degree of A.B. in 1915. He received his medical education at St. Louis University School of Medicine, graduating in 1919. For two years

thereafter, he served on rotating services of the St. Louis City Hospital, and then entered general practice in Toledo. His work had been devoted chiefly to Internal Medicine and Tuberculosis since 1924. His appointments included Director of the Department of Medicine, Mercy Hospital; Assistant Director of the Department of Medicine, Lucas County Hospital. He was a member of the Toledo and Lucas County Academy of Medicine, the Ohio State Medical Association and the American Medical Association. He became a Fellow of the American College of Physicians on March 22, 1931.

#### DR. EDWARD W. MEIS

Dr. Edward W. Meis (Fellow), Sioux City, Iowa, died December 7, 1932, of carcinoma of the stomach.

Dr. Meis received his medical degree from the University of Iowa College of Medicine in 1900. At the time of his death, he was Senior Examiner for the Prudential and Missouri State Life Insurance Companies; a member of the Sioux City Chest Clinic; a member of the staff of St. Joseph's Mercy Hospital.

He was a member of the Woodbury County Medical Society, the Iowa State Medical Association and the

American Medical Association. He became a Fellow of the American College of Physicians on February 24, 1920, and had served actively throughout his entire membership.

#### DR. FRANKLIN E. MURPHY

Dr. Franklin E. Murphy (Fellow), Kansas City, Mo., died, February 20, 1933, of heart disease; aged, 67 years.

Dr. Murphy was born November 21, 1866, at Reddington, Ind., the son of a physician. His family moved successively from Reddington to Independence, Mo., and then to Kansas City, where he received his secondary school training in the Central High School. Dr. Murphy continued his studies at the Philadelphia College of Pharmacy, graduating in 1888. After acting as a pharmacist for one year, he entered the University of Pennsylvania School of Medicine, from which he graduated in 1893. From 1896 to 1901, he was Secretary of the Kansas City Medical College; from 1901 to 1903, he pursued postgraduate work in the Universities of Göttingen, Jena, Berlin and Vienna. Shortly after his return to this country, he became Professor of Clinical Medicine in the University of Kansas School of Medicine, serving in this capacity from 1905 to 1933.

Dr. Murphy was President of the Jackson County (Mo.) Medical Society, a member of the Missouri State

Medical Association and a Fellow of the American Medical Association. He had been a Fellow of the American College of Physicians since 1920. He was a member of the Staffs of the Bell Memorial, Research, Wesley and General Hospitals.

"His record shows the career of a man who chose his profession with a full knowledge of its difficulties and trials, and steadily pursued his course of primary, professional and postgraduate instruction. This is evidence of his determination of character, as he had to earn his own way. His professional ability was recognized by members of the profession, and he was appointed to responsible positions as a teacher of medicine and elected to executive responsibilities in medical organizations."

"... Franklin E. Murphy was a man of positive character. No one, friend or enemy, was ever heard to speak of him except in terms of respect. He always took his work seriously and was a hard, patient and methodical worker. His patients all respected him and those with whom he came in intimate contact loved him." Dr. Murphy was a man who could always be relied upon to support the best traditions of the profession.

(Furnished by A. COMINGO GRIFFITH, M.D., F.A.C.P., Governor for Missouri.)

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*Natural Mineral Water*

## INDICATIONS

In stomach and liver affections and digestive disorders in general; in gout, arthritis associated with uric acidemia, uricemia, and nephrolithiasis of uric acid origin.



BOTTLED  
AT THE SPRING  
VICHY, FRANCE

## ANALYSIS (GRAMS PER LITER)

Sodium bicarbonate	3.3090
Potassium bicarbonate	0.2490
Lithium bicarbonate	0.0281
Calcium bicarbonate	0.7400
Magnesium bicarbonate	0.1016
Ferrous bicarbonate	0.0012
Sodium chloride	0.3830
Sodium sulphate	0.2430
Silica	0.0300
Sodium arseniate, Phosphate and nitrate	} present

Brochure with Therapeutic Data and Medical Bibliography  
sent on request.

Sole United States Agents, American Agency of French Vichy, Inc., 503 Fifth Ave., New York

# ANNALS OF INTERNAL MEDICINE

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